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Diffuse large B-cell lymphoma: A consensus practice statement from the Australasian Lymphoma Alliance.

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype, accounting for 30-40% of lymphoma diagnoses. Though aggressive, cure is achievable in approximately 60% of cases with primary chemo-immunotherapy, and in a further substantial minority by salvage therapy and autologous stem cell transplantation. Despite promising activity in early phase clinical trials, no intensified or novel treatment regimen has improved outcomes over R-CHOP21 in randomised studies. However, there remain several areas of controversy including the most appropriate prognostic markers, CNS prophylaxis and the optimal treatment for patients with high-risk disease. This position statement presents an evidence-based synthesis of the literature for application in Australasian practice.

KEY WORDS

DLBCL, diagnosis, prognosis, management

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INTRODUCTION

Current controversies in DLBCL include identification of biomarkers for prognostication and treatment selection and management of specific risk groups such as limited stage disease, high-risk disease, and those at risk of central nervous system (CNS) dissemination. This practice statement provides healthcare professionals with an evidence-based approach to the investigation and management of DLBCL in the Australasian setting. Specific subtypes of extranodal disease are outside the scope of this statement.

METHODOLOGY

This Consensus Practice Statement was undertaken by a panel of lymphoma experts with particular interest in DLBCL under the auspices of the Australasian Lymphoma Alliance (ALA) in accordance with the ALA Consensus Practice Statement development policy (supplementary material).

INCIDENCE AND AETIOLOGY

The incidence of non-Hodgkin lymphoma (NHL) in Australia is approximately 20 cases per 100,000 person-years and is increasing, with DLBCL accounting for 30-40%.[1] Most patients are aged over 50 years at diagnosis with a slight male predominance. The aetiology is largely unclear, though immunosuppression and Epstein-Barr virus play a role in certain cases.[2]

DIAGNOSIS

Definitive diagnosis of DLBCL relies on biopsy. Excisional node biopsy is preferred, though core biopsy may be adequate in many cases.[3] Histologically, normal lymph node architecture is usually completely or partially effaced by a diffuse proliferation of large atypical lymphoid cells, which morphologically may be classified as centroblastic, immunoblastic or anaplastic.[4] Immunohistochemistry (IHC) and flow cytometry confirm the lineage of the neoplastic lymphoid cells. The neoplastic B cells are positive for B cell markers including CD20 which has therapeutic implications.[4] Other important IHC markers are shown in Table 1. The definitive final pathological classification of DLBCL, not otherwise specified (NOS) relies upon the exclusion of high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBL-DH or HGBL-TH) by performing fluorescence in-situ hybridisation (FISH). Approximately 8% of cases resembling DLBCL morphologically are HGBL-DH when investigated for the presence of these gene rearrangements and the preferred approach is to test all cases.[5,6] If limited resources preclude routine FISH studies, testing only CD10 positive cases that concurrently express MYC and BCL2/BCL6 protein by IHC will capture most HGBL-DH whilst reducing the number of DLBCL proceeding to FISH.[6,7] Cases undergoing FISH may also utilise a stepwise approach by first testing *MYC* and, if present, subsequently testing for *BCL2* and *BCL6*. It is worth noting that FISH does not capture all cases with a HGBL-DH gene signature, which is prognostically relevant, though gene expression profiling is not routinely available.[8]

Recommendations:

- **Excisional lymph node biopsy is recommended for diagnosis, though core biopsy may be adequate in many cases. Fine needle aspiration is inadequate. (I, A)**
- **All biopsies should be reviewed by a histopathologist with lymphoma expertise (I, A)**
- **FISH for *MYC +/- BCL2 and BCL6* should ideally be performed on all cases, with rearrangement partner established where feasible (II, A)**

STAGING AND INITIAL WORK-UP

Thorough and expedient work-up of DLBCL is critical. Recommended work-up is in Table 2. Patients with highly symptomatic, bulky or clinically aggressive disease may require inpatient work-up to expedite delivery of chemotherapy. Pre-phase corticosteroids may also be required.

Recommendations:

- **Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) combined with computed tomography (CT) is the staging modality of choice, with stage assigned by the Lugano classification (table 3) (I, A).[9]**
- **All cases should be discussed in a lymphoma multidisciplinary meeting (IV, A)**
- **MRI brain and spine and cerebrospinal fluid analysis is recommended for patients at high risk of CNS involvement (e.g. CNS-IPI ≥4, multiple extranodal sites; see CNS prophylaxis section) (III-2, A).[10]**
- **FDG-PET is adequate staging for concordant marrow involvement, though biopsy may identify discordant low-grade lymphoma and can be considered when this will alter management (I, B).[11]**
- **Counselling regarding contraception, menstrual management, pregnancy screening and fertility preservation should occur prior to administration of chemotherapy where clinically appropriate (IV, A).**

PROGNOSTIC FACTORS

IPI and clinical factors

Several prognostic tools discriminate DLBCL risk groups. The original International Prognostic Index (IPI) and the age-adjusted IPI (aaIPI)[12] were first described in the pre-rituximab era, but the same factors maintain prognostic significance in the rituximab era (revised-IPI).[13] The NCCN-IPI incorporates specific extranodal involvement, LDH and age to better stratify DLBCL risk when treated with R-CHOP (Table 4).[14]

Tumour bulk (≥7.5cm in maximal diameter) has been associated with poor prognosis in R-CHOP-treated patients.[15] Bone marrow, testicular, adrenal, renal, uterine involvement, primary breast DLBCL and high IPI are independently associated with higher CNS relapse risk.[16]

Molecular biology and biomarkers

Numerous pathobiological factors have been identified that add prognostic value to the IPI. The following have the most comprehensive data.

Cell of Origin (COO)

Gene expression profiling (GEP) identifies least three distinct molecular subtypes of DLBCL, arising at the various stages of differentiation. These are the germinal centre B-cell like (GCB), activated B-cell like (ABC) and an unclassifiable group.[17] When tested via GEP there is a clear and reproducible negative prognostic impact of the ABC subtype.[17,18]

The reported impact of IHC-assigned COO has been inconsistent, though probably retains some prognostic value.[19] The Hans algorithm (Figure 1) is most frequently used due to simplicity, availability and relative concordance with GEP.[20]

Protein expression

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The dual expression (DE) of MYC (≥40%) and BCL2 (≥50%) proteins by IHC has shown prognostic significance independent of the IPI and COO; indeed it has been suggested that DE-DLBCL accounts for the poor outcomes of ABC-type DLBCL where DE is more common.[17,21,22]

Chromosomal translocation

Single translocations involving solely *MYC, BCL2* or *BCL6* have not been consistently associated with prognosis. FISH studies showing *MYC* and *BCL2* and/or *BCL6* rearrangements define the entity HGBL-DH or HGBL-TH in the WHO 2016 classification and are generally associated with a poor prognosis.[4] However, the original retrospective studies suffered from selection bias, with unselected registry-based testing showing a more favourable outlook (5yr PFS ~58%, 5yr OS ~60%). The *MYC* translocation partner also appears of prognostic relevance, with translocations to an immunoglobulin gene (Ig) conferring the highest risk and a non-Ig partner conferring no additional risk; thus assessment of the break partner should be performed if feasible.[23]

Figure 2 demonstrates the relationship between COO, antigen overexpression and rearrangement of MYC and BCL2.[24]

Interim PET

Interim FDG-PET (iPET) has been assessed for its prognostic benefit and subsequent therapeutic implications. Although data are conflicting, most recent studies demonstrate a clear and independent association between iPET positivity and inferior outcomes.[25-29] The most robust prognostic measure appears to be the change in maximum standard uptake value (ΔSUVmax) after 4 cycles of R-CHOP; Deauville scores of 5 at this timepoint also predict refractory disease.[30,31] FDG-PET following two cycles also has prognostic importance and can predict early progression.[32] No randomised study has demonstrated a benefit of dose escalation based upon iPET and thus no recommendation for change in therapy based upon iPET can be made for routine clinical practice.[32,33] There is insufficient evidence to support de-escalation of therapy for early responders.

Recommendations:

- **The IPI should be recorded in all patients with DLBCL and the NCCN-IPI provides the best discrimination between prognostic groups (I, A).[34]**
- **COO should be determined in all cases of DLBCL and with specification of the method used (I, A).[4]**
- **All patients should have IHC for MYC and BCL2 (I, B)**
- **Interim FDG-PET adds prognostic value and may be performed following two or four cycles of R-CHOP (I, C)**
- **Primary therapy should be completed provided there has been at least a partial response on interim FDG-PET (I, B)**

TREATMENT

Primary chemo-immunotherapy

Standard treatment with chemo-immunotherapy results in OS rates of approximately 70%, 60%, and 45% at 3, 5, and 10 years respectively.[34]

All patients should receive rituximab in combination with chemotherapy given its addition confers a significant survival advantage with little additional toxicity.[35-39] The combination of rituximab with

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CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) is the standard regimen for most patients with DLBCL due to efficacy and tolerability.[40-44]

In unselected DLBCL, R-CHOP given every 21 days (R-CHOP21) showed equivalent efficacy with improved tolerability compared to a 14 day schedule (R-CHOP14) and remains the recommended front-line treatment.[45-47] For patients with advanced-stage disease, six cycles provides similar efficacy to eight.[39,48] There is no role for consolidation autologous stem cell transplantation (autoHCT) or maintenance therapy post R-CHOP for patients achieving complete metabolic response (CMR) due to absence of overall survival advantage.[49-53]

Recommendations:

- **6 cycles of R-CHOP21 is recommended for first-line advanced-stage DLBCL (I, A).**
- **Timely, full dose therapy should be delivered in patients <80 years of age where organ function and toxicity allow (III-1, A).[48]**
- **AutoHCT or maintenance therapy should not be used to consolidate DLBCL in complete metabolic remission following R-CHOP (I, A).**
- **For patients with limited stage, non-bulky (<7.5cm), IPI 0 disease 4 cycles of R-CHOP21 followed by 2 cycles of rituximab monotherapy is equivalent to 6 cycles (II, A).**

<u>Consolidation radiation therapy</u>

Radiation therapy (RT) is an effective locoregional consolidative therapy for DLBCL. Consolidation RT is most useful where risk of local relapse is the dominant site of failure, even after effective systemic therapy.

Primary indications for RT in first-line management of nodal DLBCL include (i) chemotherapy minimisation strategy in non-bulky limited-stage disease,[54,55] (ii) to consolidate sites at high risk of local relapse (e.g. bulky disease ≥7.5cm),[56,57] and (iii) to convert partial metabolic responses to complete response after initial chemoimmunotherapy.[58] Indications for RT in extra-nodal DLBCL sites are presented in other international guidelines.[59]

In general, doses of 30-36Gy are recommended to consolidate sites in CMR, delivered in 1.5-2Gy per fraction.[60,61] Doses of 36-50Gy may be required for FDG-PET-avid residual masses.[61]

Limited stage disease (non-bulky)

Conventional treatment approaches for non-bulky, limited stage disease include either (i) full course chemo-immunotherapy (6 cycles of R-CHOP),[56,62] or (ii) abbreviated chemo-immunotherapy (3-4 cycles of R-CHOP) with consolidation involved site RT (ISRT).[54,63,64] Where tolerated, full course chemo-immunotherapy is the preferred strategy for patients with higher risk disease, based on the continued pattern of late relapses observed following abbreviated systemic therapy in patients with stage-adjusted IPI ≥1.[63] However, for patients who may not tolerate full course chemo-immunotherapy, abbreviated chemo-immunotherapy and 30 Gy ISRT offers equivalent survival outcomes[63] with reduced chemo-toxicity and acceptable radiation-induced toxicity profile.[55,60,64,65]

For young (≤60 yrs) low-risk patients (aaIPI 0), four cycles of R-CHOP21 and two additional dose of rituximab without RT is non-inferior to 6 cycles of R-CHOP, with expected reduction in toxicity.[66] For patients >60 no other IPI risk factors, abbreviated chemotherapy without radiotherapy may also be a reasonable option in patients with a negative iPET, but this approach has not been subjected to a

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randomised study.[67] This approach is probably not suitable for patients with additional IPI risk factors where the preferred approach is six cycles of R-CHOP.[68]

Bulk

Several studies in the pre-FDG-PET era have demonstrated the benefit of consolidation RT to bulky or extranodal sites.[56,69] Omission of RT to original sites of bulk that achieve CMR by end of chemo-immunotherapy but have an incomplete CT response remains an area of controversy; the results of PET-adapted randomised studies are awaited (e.g. OPTIMAL>60, NCT01478542). Patients with bulky disease should not have systemic therapy abbreviated.

Recommendations:

- **ISRT is recommended over involved field RT due to equivalent efficacy and lower toxicity (I, A).[64]**
- **For patients with limited stage disease and stage-adjusted IPI ≥1, ISRT should be considered if it is necessary to abbreviate chemo-immunotherapy, e.g. for toxicity (II-B), though the preferred strategy remains 6 cycles of R-CHOP[54,63,70]**
- **ISRT remains standard of care for original sites of bulk (≥7.5cm) with incomplete CT resolution following R-CHOP (II,B), although omission of ISRT in PET-negative patients may be reasonable if toxicity is prohibitive (III-2,B).[71]**
- **ISRT is recommended to sites of incomplete metabolic response on FDG-PET unless other salvage is planned and if the disease is encompassable (III-2, A).**
- **For patients ≤60 with aaIPI=0, low-bulk, limited stage disease with CMR at chemo-immunotherapy completion, radiotherapy may be omitted (I,A).[66] A similar approach in patients >60yrs may be considered after a discussion of risks and benefits (III-2, C).[67]**

<u>Poor risk disease</u>

No randomised trial data supports using intensive regimens over R-CHOP21. However, such studies have not been powered to address patients with high clinical risk scores (e.g. aaIPI 2-3), so the question of whether intensified regimens improve outcomes for patients with both advanced-stage and high IPI disease has not been definitively answered.[45,46,72] R-CHOEP14 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) has shown relatively favourable outcomes in younger, high-risk patients but has not been compared with R-CHOP21 directly.[73]

The poor outcome of advanced-stage HGBL-DH, frequent association with other high risk clinical factors, and poor chance of salvage upon treatment failure has led to the widespread but speculative adoption of more intensive chemotherapy regimens such as R-DA-EPOCH and R-CHOEP14 with or without high dose autoHCT consolidation in first remission. Evidence for such approaches is limited to retrospective studies which suggest a higher CR rate following intensified induction, and which show no clear advantage to autoHCT in first complete response.[74,75]

Recommendations:

- **Patients with high biological risk should be enrolled in clinical trials where possible.**
- **No alteration of treatment strategy is recommended based on COO, DE or lone *MYC* rearrangement (I, A).**

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- **Intensification to R-DA-EPOCH or R-CHOEP14 in younger fit patienst with aaIPI 2-3 and in HGBL-DH may be justified in selected cases following discussion about the risks and benefits (III-2, C)**

Management of Elderly Patients with DLBCL

The potential for cure is reduced in the elderly due to increased likelihood of aggressive disease biology, medical comorbidities, functional decline and reduced tolerance of intensive chemotherapy.[76,77] There is no universally accepted definition of 'elderly' DLBCL patients in the literature. Until recently elderly patients with DLBCL were under-represented in clinical trials, thus the optimal treatment for these patients remains unclear.

For fit older patients <80yrs, six cycles of R-CHOP21 is suggested with supportive measures as listed below, and geriatric assessment tools may assist in determining fitness.[78] For patients >80yrs or those unfit for full dose R-CHOP21, R-mini-CHOP is a reasonable option with a reported 2-year OS and PFS of 59% and 47% respectively.[79] For unfit or frail patients regimens such as R-GCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone),[80] R-mini-CEOP (with epirubicin)[81] or R-CEEP (rituximab, cyclophosphamide, epirubicin, etoposide, prednisolone)[82] can be considered. R-CEOP (with etoposide) is an option for patients ineligible for an anthracycline.[83]

Recommendations:

- **The use of a geriatric assessment tool is recommended to guide treatment choice in elderly DLBCL patients (IV, C)**
- **Pre-phase prednisone is recommended in elderly patients (III-2, B).[84]**
- **Prophylactic G-CSF is recommended for all cycles of therapy (III, B).[85]**
- **Vitamin D supplementation should be considered in deficient patients (IV, C).[86-88]**
- **For fit older patients six cycles of R-CHOP21 is recommended with the above supportive measures (I,A).[78]**
- **For patients >80yrs or those unfit for R-CHOP21, R-mini-CHOP is a reasonable option (III-2, B)**
- **Abbreviated therapy (3-4 cycles of R-CHOP) plus ISRT can be considered in elderly patients with limited stage, non-bulky disease (II-B).**

Synchronous CNS/systemic disease

Patients presenting with synchronous CNS involvement at first presentation of systemic DLBCL have a poor prognosis driven largely by the CNS disease.[10] Some data support the use of AutoHCT in first complete remission, although the benefit is unclear if primary induction therapy includes high-dose methotrexate and cytarabine.[10,89] Recently published prospective trials taking an intensive induction approach with or without consolidative AutoSCT had relatively favourable outcomes in this group.[90,91] Intrathecal therapy can be added in those with leptomeningeal disease, and consolidation with radiotherapy and autoHCT at the discretion of the treating clinician is based upon disease response and patient factors.

Recommendations:

- **Patients with synchronous CNS and systemic DLBCL at diagnosis should receive a combination chemotherapy regimen that includes high-dose intravenous methotrexate and cytarabine as well as standard chemo-immunotherapy, which is**

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usually achieved with alternating treatment cycles. Consideration may be given to consolidation AutoHCT and RT (III-2, B).

CNS prophylaxis

Unselected DLBCL carries ~5% risk of CNS relapse and patients at high risk should be identified at diagnosis.[92] The most commonly used clinical risk score is the CNS-IPI which adds renal and adrenal involvement to the standard IPI factors to identify patients at high risk of CNS relapse.[93] However, a high-risk score (≥4) only identifies 55% of patients who will experience CNS relapse and we therefore also consider patients with >2 extranodal sites as high-risk.[94] Additional specific extranodal DLBCL sites appear to carry an independent CNS risk including testis, uterus and breast.[95-97] Certain biological features also appear to increase the risk of CNS presentations, including ABC subtype (particularly C5/MCD types),[98-100] DE-DLBCL and possibly HGBL-DH.[75,101]

The role of CNS prophylaxis is controversial with conflicting data and forthcoming randomised clinical trials are unlikely due to the relative infrequency of events. Recent retrospective analyses casts doubt on the benefit of intravenous methotrexate prophylaxis, though were likely underpowered.[102] Intensive systemic regimens with inbuilt CNS-penetrating agents and the administration of high-dose intravenous methotrexate appear to lower the risk of CNS progression; the latter with less associated toxicity.[103-105]

Recommendations:

- **Intrathecal methotrexate prophylaxis is not recommended unless systemic prophylaxis is not deliverable (III-2, B).[104,106]**
- **2-3 cycles of high-dose intravenous methotrexate (e.g. 3g/m^2) in addition to R-CHOP21 is reasonable in patients with high CNS-IPI and those with multiple or specific extranodal sites (III-2, C).[104,105]**
- **CNS prophylaxis in patients with high biological risk DLBCL but low- or intermediate-risk CNS-IPI scores should be discussed on a case-by-case basis.**
- **CNS-penetrant therapy may be delivered at the completion of or intercalated with R-CHOP, , though an intercalated approach may increase toxicity and compromise R-CHOP delivery.[107]**

RESPONSE ASSESSMENTA ND FOLLOW UP

Following completion of induction chemo-immunotherapy, patients should be re-evaluated to confirm disease response. The EOT imaging modality of choice is FDG-PET/CT, which may also be helpful in guiding RT dose prescription and planning.[108]

Upon achieving CMR, conventional practice is for 5 years of follow up for monitoring of complications of therapy and disease relapse.[109] Surveillance imaging for relapse detection is low yield and confers no survival advantage compared with clinically detected relapse. Therefore, the current surveillance strategy centres on clinical and laboratory findings, with imaging indicated only when there is clinical suspicion of relapse. Interval FDG-PET may be employed in cases where the EOT FDG-PET is equivocal.

Recommendations:

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- **EOT FDG-PET/CT should be performed at least 3 weeks, and preferably 6-8 weeks after completion of chemo-immunotherapy, and 8-12 weeks after the completion of RT.[108]**
- **We recommend defining complete metabolic remission in accordance with the Lugano classification (I, A).[9]**
- **Imaging for the detection of relapse should be performed due to clinical suspicion rather than surveillance (III-2, B).[110,111]**

RELAPSED/REFRACTORY (R/R) DLBCL: TRANSPLANT ELIGIBLE PATIENTS

In transplant-eligible patients experiencing first relapse/progression, salvage chemo-immunotherapy followed by autoHCT provides a survival benefit over salvage therapy alone.[112] Disease response as determined by FDG-PET is the most critical factor in proceeding to autoHCT, and depth of response pre-transplant correlates with post-transplant outcomes.[113] There is no routine role for allogeneic transplantation in second complete remission.[114]

The commonly used salvage and autoHCT conditioning regimens are summarised in table 5a and 5b though there are currently insufficient data to recommend one over another. The only two randomised studies failed to show a difference in response or survival for R-ICE vs R-DHAP and R-DHAP vs R-GDP respectively, though R-DHAP appears more toxic.[115,116] Additionally, ofatumumab offered no benefit over Rituximab with a DHAP backbone.[113] There is no benefit to rituximab maintenance following autoHCT.[117]

Radiotherapy before or after autoHCT to consolidate responses should be decided on a case-by-case basis, typically where all sites of disease can be addressed within a radiation field. Guidelines were recently published by ILROG.[118]

Myeloablative conditioning regimens for autologous HCT have not been directly compared in prospective trials. BEAM is the most commonly used regimen.[119]

Recommendations:

- **In patients experiencing first relapse/progression who are eligible for high-dose chemotherapy with autoHCT, we recommend salvage chemo-immunotherapy followed by autoHCT (I, A)**

- **Sensitivity to salvage chemo-immunotherapy as determined by FDG-PET is a prerequisite to proceeding to autoHCT due to high failure rates with chemoresistance (III-2, A).[120-124]**

- **Consideration should be given to alternative or additional salvage strategies for responding patients failing to achieve CR by FDG-PET prior to autoSCT. Options including proceeding to AutoSCT, radiotherapy, CAR-T cells and clinical trial should be decided on a case-by-case basis (III-2, C).**

R/R DLBCL: TRANSPLANT INELIGIBLE PATIENTS

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The management of R/R DLBCL in transplant ineligible patients is often non-curative, though a proportion of patients with refractory disease encompassable in a single RT field may be cured by this approach.[125] For the remainder, there is no standard approach, and thus we recommend early consideration of active clinical trials where available. Chimeric Antigen Receptor T cell therapy (CAR-T) beyond second-line treatment can offer durable remissions and probably cure in 30-40% of treated patients. CAR-T are approved in Australia in patients who have relapsed or who are refractory to at least 2 lines of systemic treatment, and who have relapsed or are ineligible for a transplant. However, the complexity of the procedure precludes its use in many patients, especially those with refractory lymphoma or medical comorbidities.[126,127] Whilst an in-depth discussion of this topic falls outside the scope of this manuscript, it is recommended that an early discussion with a CAR-T centre should be considered where clinically appropriate.

For many patients, a potentially curative option is unavailable, and the goal of therapy is disease control and quality of life, thus more intensive salvage regimens are usually inappropriate. Gemcitabine-based regimens offer a reasonable combination of efficacy and tolerability.[128-133] Novel agents such as polatuzumab-vedotin with bendamustine and lenalidomide may provide additional options in selected cases, pending regulatory approval/reimbursement in Australia.[134,135] Radiotherapy and high-dose corticosteroid may provide symptom palliation. Higher dose RT may achieve durable remissions in the uncommon circumstance of localised R/R DLBCL.[59]

Recommendations:

- **We recommend enrolment in clinical trials as the first option where available for transplant ineligible R/R DLBCL patients**
- **CAR-T therapy provides a potentially curative option for some patients and early discussion with a CAR-T center is recommended if this approach is considered.**
- **RT should be considered for patients with limited-stage relapse**

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

An immense amount of research has been conducted in DLBCL since the introduction of rituximab without significant improvement in outcomes. Several studies have investigated the addition of novel agents to patients with poor biological risk tumours without a survival advantage.[136-138] As our understanding of the genetic and functional drivers of DLBCL increases, clinical trial design needs to evolve to address not only those patients with poor prognostic disease, but rational drug combinations that target pathogenic mechanisms.

Antibody-drug conjugates such as polatuzumab-vedotin clearly have activity in relapsed and refractory disease and are currently being investigated in the up-front setting (NCT03274492). While CAR-T therapy is approved in the third line-setting, ongoing trials are actively exploring their role in high-risk first relapse in the transplant-eligible population. Bispecific T-cell engaging antibodies also show significant promise in chemo-refractory disease.

Improving access to treatment for certain subgroups such those from regional and remote areas remains a challenge and the use of telehealth and teletrials technology may improve the disparate outcomes for these patients.

Methodology

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These consensus practice statements were developed in accordance with the Australasian Lymphoma Alliance (ALA) policy for Consensus Practice Statement development. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the NHMRC evidence hierarchy shown in tables 6 and 7.[139] Statements without grading were considered justified standard clinical practice by the experts and the ALA members. The manuscript has been subjected to an anonymous peer review process.

References

1. Bufton B, Kilo R, Wong H, H. R, Harvey J, Moon L. *Cancer in Australia.* Australian Institute of Health and Wellbeing2019.
2. Dharnidharka VR, Webster AC, Martinez OM, Preiksaitis JK, Leblond V, Choquet S. Post-transplant lymphoproliferative disorders. *Nat Rev Dis Primers.* 2016;2:15088.
3. Johl A, Lengfelder E, Hiddemann W, Klapper W, German Low-grade Lymphoma Study G. Core needle biopsies and surgical excision biopsies in the diagnosis of lymphoma-experience at the Lymph Node Registry Kiel. *Ann Hematol.* 2016;95(8):1281-1286.
4. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390.
5. Pedersen MO, Gang AO, Poulsen TS, et al. Double-hit BCL2/MYC translocations in a consecutive cohort of patients with large B-cell lymphoma - a single centre's experience. *Eur J Haematol.* 2012;89(1):63-71.
6. Scott DW, King RL, Staiger AM, et al. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with diffuse large B-cell lymphoma morphology. *Blood.* 2018;131(18):2060-2064.
7. Merron B, Davies A. Double hit lymphoma: How do we define it and how do we treat it? *Best Pract Res Clin Haematol.* 2018;31(3):233-240.
8. Ennishi D, Jiang A, Boyle M, et al. Double-Hit Gene Expression Signature Defines a Distinct Subgroup of Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2019;37(3):190-201.
9. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.
10. Wight JC, Yue M, Keane C, et al. Outcomes of synchronous systemic and central nervous system (CNS) involvement of diffuse large B-cell lymphoma are dictated by the CNS disease: a collaborative study of the Australasian Lymphoma Alliance. *Br J Haematol.* 2019;187(2):174-184.
11. Khan AB, Barrington SF, Mikhaeel NG, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. *Blood.* 2013;122(1):61-67.
12. Shipp MA, Harrington DP. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med.* 1993;329(14):987-994.
13. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood.* 2007;109(5):1857-1861.
14. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood.* 2014;123(6):837-842.
15. Pfreundschuh M, Ho AD, Cavallin-Stahl E, et al. Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated

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with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study. *Lancet Oncol.* 2008;9(5):435-444.
16. Fletcher CD, Kahl BS. Central nervous system involvement in diffuse large B-cell lymphoma: an analysis of risks and prevention strategies in the post-rituximab era. *Leuk Lymphoma.* 2014;55(10):2228-2240.
17. Scott DW, Mottok A, Ennishi D, et al. Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies. *J Clin Oncol.* 2015;33(26):2848-2856.
18. Vitolo U, Trneny M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2017;35(31):3529-3537.
19. Read JA, Koff JL, Nastoupil LJ, Williams JN, Cohen JB, Flowers CR. Evaluating cell-of-origin subtype methods for predicting diffuse large B-cell lymphoma survival: a meta-analysis of gene expression profiling and immunohistochemistry algorithms. *Clin Lymphoma Myeloma Leuk.* 2014;14(6):460-467 e462.
20. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004;103(1):275-282.
21. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol.* 2012;30(28):3452-3459.
22. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood.* 2013;121(20):4021-4031.
23. Rosenwald A, Bens S, Advani R, et al. Prognostic Significance of MYC Rearrangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium. *J Clin Oncol.* 2019;37(35):3359-3368.
24. Wight JC, Chong G, Grigg AP, Hawkes EA. Prognostication of diffuse large B-cell lymphoma in the molecular era: moving beyond the IPI. *Blood Rev.* 2018;32(5):400-415.
25. Yang DH, Ahn JS, Byun BH, et al. Interim PET/CT-based prognostic model for the treatment of diffuse large B cell lymphoma in the post-rituximab era. *Ann Hematol.* 2013;92(4):471-479.
26. Wu X, Pertovaara H, Korkola P, et al. Early interim PET/CT predicts post-treatment response in diffuse large B-cell lymphoma. *Acta Oncol.* 2014;53(8):1093-1099.
27. Nols N, Mounier N, Bouazza S, et al. Quantitative and qualitative analysis of metabolic response at interim positron emission tomography scan combined with International Prognostic Index is highly predictive of outcome in diffuse large B-cell lymphoma. *Leuk Lymphoma.* 2014;55(4):773-780.
28. Pardal E, Coronado M, Martin A, et al. Intensification treatment based on early FDG-PET in patients with high-risk diffuse large B-cell lymphoma: a phase II GELTAMO trial. *Br J Haematol.* 2014;167(3):327-336.
29. Lanic H, Mareschal S, Mechken F, et al. Interim positron emission tomography scan associated with international prognostic index and germinal center B cell-like signature as prognostic index in diffuse large B-cell lymphoma. *Leuk Lymphoma.* 2012;53(1):34-42.
30. Hertzberg M. High-risk DLBCL: interim PET? Not yet. *Blood.* 2017;130(11):1277-1278.
31. Hertzberg M, Gandhi MK, Trotman J, et al. Early treatment intensification with R-ICE and 90Y-ibritumomab tiuxetan (Zevalin)-BEAM stem cell transplantation in patients with high-risk diffuse large B-cell lymphoma patients and positive interim PET after 4 cycles of R-CHOP-14. *Haematologica.* 2017;102(2):356-363.

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32. Duhrsen U, Muller S, Hertenstein B, et al. Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL): A Multicenter, Randomized Phase III Trial. *J Clin Oncol.* 2018;36(20):2024-2034.
33. Casasnovas RO, Ysebaert L, Thieblemont C, et al. FDG-PET-driven consolidation strategy in diffuse large B-cell lymphoma: final results of a randomized phase 2 study. *Blood.* 2017;130(11):1315-1326.
34. Ruppert AS, Dixon JG, Salles G, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. *Blood.* 2020;135(23):2041-2048.
35. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood.* 2010;116(12):2040-2045.
36. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 2005;23(18):4117-4126.
37. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol.* 2006;24(19):3121-3127.
38. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2011;12(11):1013-1022.
39. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol.* 2008;9(2):105-116.
40. Bartlett NL, Petroni GR, Parker BA, et al. Dose-escalated cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (CHOPE) chemotherapy for patients with diffuse lymphoma: Cancer and Leukemia Group B studies 8852 and 8854. *Cancer.* 2001;92(2):207-217.
41. Björkholm M, Andersson T, Ahlbom A, Ösby E. CNOP (mitoxantrone) chemotherapy is inferior to CHOP (doxorubicin) in the treatment of patients with aggressive non-Hodgkin lymphoma (meta-analysis). *Eur J Haematol.* 2008;80(6):477-482.
42. Burton C, Smith P, Vaughan-Hudson G, et al. Comparison of CHOP versus CIOP in good prognosis younger patients with histologically aggressive non-Hodgkin lymphoma. *Br J Haematol.* 2005;130(4):536-541.
43. Gaynor ER, Unger JM, Miller TP, et al. Infusional CHOP chemotherapy (CVAD) with or without chemosensitizers offers no advantage over standard CHOP therapy in the treatment of lymphoma: a Southwest Oncology Group Study. *J Clin Oncol.* 2001;19(3):750-755.
44. Sparano JA, Weller E, Nazeer T, et al. Phase 2 trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with poor-prognosis, intermediate-grade non-Hodgkin lymphoma: an Eastern Cooperative Oncology Group trial (E3493). *Blood.* 2002;100(5):1634-1640.
45. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet.* 2013;381(9880):1817-1826.
46. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(6):525-533.

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47. Kamel S, O'Connor S, Lee N, Filshie R, Nandurkar H, Tam CS. High incidence of Pneumocystis jirovecii pneumonia in patients receiving biweekly rituximab and cyclophosphamide, adriamycin, vincristine, and prednisone. *Leuk Lymphoma.* 2010;51(5):797-801.
48. Marangolo M, Bengala C, Conte PF, et al. Dose and outcome: the hurdle of neutropenia (Review). *Oncol Rep.* 2006;16(2):233-248.
49. Cortelazzo S, Tarella C, Gianni AM, et al. Randomized Trial Comparing R-CHOP Versus High-Dose Sequential Chemotherapy in High-Risk Patients With Diffuse Large B-Cell Lymphomas. *J Clin Oncol.* 2016;34(33):4015-4022.
50. Epperla N, Hamadani M, Reljic T, Kharfan-Dabaja MA, Savani BN, Kumar A. Upfront autologous hematopoietic stem cell transplantation consolidation for patients with aggressive B-cell lymphomas in first remission in the rituximab era: A systematic review and meta-analysis. *Cancer.* 2019;125(24):4417-4425.
51. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 2013;369(18):1681-1690.
52. Morrison VA, Weller EA, Habermann TM, et al. Maintenance rituximab (MR) compared to observation (OBS) after R-CHOP or CHOP in older patients (pts) with diffuse large B-cell lymphoma (DLBCL): An Intergroup E4494/C9793 update. *J Clin Oncol.* 2007;25(18_suppl):8011-8011.
53. Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide Maintenance Compared With Placebo in Responding Elderly Patients With Diffuse Large B-Cell Lymphoma Treated With First-Line Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. *J Clin Oncol.* 2017;35(22):2473-2481.
54. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol.* 2008;26(14):2258-2263.
55. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy Alone Compared with Chemotherapy plus Radiotherapy for Localized Intermediate- and High-Grade Non-Hodgkin's Lymphoma. *N Engl J Med.* 1998;339(1):21-26.
56. Pfreundschuh M, Murawski N, Ziepert M, et al. Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients: Results of the 2x2 randomized UNFOLDER trial of the DSHNHL/GLA. *J Clin Oncol.* 2018;36(15_suppl):7574-7574.
57. Held G, Murawski N, Ziepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol.* 2014;32(11):1112-1118.
58. Dabaja BS, Hess K, Shihadeh F, et al. Positron Emission Tomography/Computed Tomography Findings During Therapy Predict Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Chemotherapy Alone but Not in Those Who Receive Consolidation Radiation. *Int J Radiat Oncol Biol Phys.* 2014;89(2):384-391.
59. Yahalom J, Illidge T, Specht L, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2015;92(1):11-31.
60. Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial. *Radiother Oncol.* 2011;100(1):86-92.
61. Wirth A, Mikhaeel NG, Aleman BMP, et al. Involved Site Radiation Therapy in Adult Lymphomas: An Overview of International Lymphoma Radiation Oncology Group Guidelines. *Int J Radiat Oncol Biol Phys.* 2020;107(5):909-933.
62. Pfreundschuh M, Kuhnt E, Trümper L, et al. Randomised Intergroup Trial of First line Treatment for young Low-Risk Patients (<61 years) with Diffuse Large B-Cell Non-Hodgkin's Lymphoma (DLBCL) with a CHOP-like Regimen with or without the Anti-CD20 Antibody Rituximab – 6-Year Follow-up of the Mint Study of the Mabthera International Trial (MInT) Group. *Blood.* 2010;116(21):111-111.

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63. Stephens DM, Li H, LeBlanc ML, et al. Continued Risk of Relapse Independent of Treatment Modality in Limited-Stage Diffuse Large B-Cell Lymphoma: Final and Long-Term Analysis of Southwest Oncology Group Study S8736. *J Clin Oncol.* 2016;34(25):2997-3004.
64. Campbell BA, Connors JM, Gascoyne RD, Morris WJ, Pickles T, Sehn LH. Limited-stage diffuse large B-cell lymphoma treated with abbreviated systemic therapy and consolidation radiotherapy. *Cancer.* 2012;118(17):4156-4165.
65. Pugh TJ, Ballonoff A, Rusthoven KE, et al. Cardiac mortality in patients with stage I and II diffuse large B-cell lymphoma treated with and without radiation: a surveillance, epidemiology, and end-results analysis. *Int J Radiat Oncol Biol Phys.* 2010;76(3):845-849.
66. Poeschel V, Held G, Ziepert M, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. *Lancet.* 2019;394(10216):2271-2281.
67. Persky DO, Li H, Stephens DM, et al. PET-Directed Therapy for Patients with Limited-Stage Diffuse Large B-Cell Lymphoma - Results of Intergroup Nctn Study S1001. *Blood.* 2019;134(Supplement_1):349-349.
68. Hawkes EA, Opat S, Hertzberg M. Caution in Expanding the Use of Abbreviated R-CHOP to Poor-Risk Limited-Stage DLBCL. *J Clin Oncol.* 2020;38(35):4221-4222.
69. Held G, Murawski N, Ziepert M, et al. Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma. *J Clin Oncol.* 2014;32(11):1112-1118.
70. Odejide OO, Cronin AM, Davidoff AJ, LaCasce AS, Abel GA. Limited stage diffuse large B-cell lymphoma: comparative effectiveness of treatment strategies in a large cohort of elderly patients. *Leuk Lymphoma.* 2015;56(3):716-724.
71. Freeman CL, Savage KJ, Villa D, et al. Long-Term Results of PET-Guided Radiation in Advanced-Stage Diffuse Large B-Cell Lymphoma Patients Treated with R-CHOP. *Blood.* 2020.
72. Bartlett NL, Wilson WH, Jung SH, et al. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *J Clin Oncol.* 2019;37(21):1790-1799.
73. Schmitz N, Nickelsen M, Ziepert M, et al. Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002-1). *Lancet Oncol.* 2012;13(12):1250-1259.
74. Landsburg DJ, Falkiewicz MK, Maly J, et al. Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission. *J Clin Oncol.* 2017;35(20):2260-2267.
75. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood.* 2014;124(15):2354-2361.
76. d'Amore F, Brincker H, Christensen BE, et al. Non-Hodgkin's lymphoma in the elderly. A study of 602 patients aged 70 or older from a Danish population-based registry. The Danish LYEO-Study Group. *Ann Oncol.* 1992;3(5):379-386.
77. Nabhan C, Smith SM, Helenowski I, et al. Analysis of very elderly (>/=80 years) non-hodgkin lymphoma: impact of functional status and co-morbidities on outcome. *Br J Haematol.* 2012;156(2):196-204.
78. Beygi S, Sadashiv S, Reilly JB, Khan C, Lister J. Frontline treatment of diffuse large B-cell lymphoma in elderly: a systematic review of clinical trials in post-rituximab era. *Leuk Lymphoma.* 2018;59(12):2847-2861.
79. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2011;12(5):460-468.
80. Fields PA, Townsend W, Webb A, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients

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with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. *J Clin Oncol.* 2014;32(4):282-287.
81. Merli F, Luminari S, Rossi G, et al. Cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab versus epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab for the initial treatment of elderly "fit" patients with diffuse large B-cell lymphoma: results from the ANZINTER3 trial of the Intergruppo Italiano Linfomi. *Leuk Lymphoma.* 2012;53(4):581-588.
82. Yeung J, Campbell A, Bryant C, et al. Safety and Efficacy of R-CEEP (Rituximab, Cyclophosphamide, Epirubicin, Etoposide, Prednisolone) in Elderly or Unfit Patients with Diffuse Large B-Cell Lymphoma (DLBCL): A Retrospective Single-Centre Experience. *Blood.* 2019;134(Supplement 1):2911.
83. Rashidi A, Oak E, Carson KR, Wagner-Johnston ND, Kreisel F, Bartlett NL. Outcomes with R-CEOP for R-CHOP-ineligible patients with diffuse large B-cell lymphoma are highly dependent on cell of origin defined by Hans criteria. *Leuk Lymphoma.* 2016;57(5):1191-1193.
84. Pfreundschuh M. How I treat elderly patients with diffuse large B-cell lymphoma. *Blood.* 2010;116(24):5103-5110.
85. Repetto L, Biganzoli L, Koehne CH, et al. EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer.* 2003;39(16):2264-2272.
86. Bittenbring JT, Neumann F, Altmann B, et al. Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. *J Clin Oncol.* 2014;32(29):3242-3248.
87. Drake MT, Maurer MJ, Link BK, et al. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. *J Clin Oncol.* 2010;28(27):4191-4198.
88. Hohaus S, Tisi MC, Bellesi S, et al. Vitamin D deficiency and supplementation in patients with aggressive B-cell lymphomas treated with immunochemotherapy. *Cancer Med.* 2018;7(1):270-281.
89. Damaj G, Ivanoff S, Coso D, et al. Concomitant systemic and central nervous system non-Hodgkin lymphoma: the role of consolidation in terms of high dose therapy and autologous stem cell transplantation. A 60-case retrospective study from LYSA and the LOC network. *Haematologica.* 2015;100(9):1199-1206.
90. Ferreri AJM, Doorduijn JK, Re A, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. *Lancet Haematol.* 2021;8(2):e110-e121.
91. McMillan AK, Phillips EH, Kirkwood AA, et al. Favourable outcomes for high-risk diffuse large B-cell lymphoma (IPI 3-5) treated with front-line R-CODOX-M/R-IVAC chemotherapy: results of a phase 2 UK NCRI trial. *Ann Oncol.* 2020;31(9):1251-1259.
92. Ghose A, Elias HK, Guha G, Yellu M, Kundu R, Latif T. Influence of Rituximab on Central Nervous System Relapse in Diffuse Large B-Cell Lymphoma and Role of Prophylaxis--A Systematic Review of Prospective Studies. *Clin Lymphoma Myeloma Leuk.* 2015;15(8):451-457.
93. Schmitz N, Zeynalova S, Nickelsen M, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. *J Clin Oncol.* 2016;34(26):3150-3156.
94. El-Galaly TC, Villa D, Michaelsen TY, et al. The number of extranodal sites assessed by PET/CT scan is a powerful predictor of CNS relapse for patients with diffuse large B-cell lymphoma: An international multicenter study of 1532 patients treated with chemoimmunotherapy. *Eur J Cancer.* 2017;75:195-203.
95. El-Galaly TC, Cheah CY, Hutchings M, et al. Uterine, but not ovarian, female reproductive organ involvement at presentation by diffuse large B-cell lymphoma is associated with poor

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outcomes and a high frequency of secondary CNS involvement. *Br J Haematol.* 2016;175(5):876-883.
96. Kridel R, Telio D, Villa D, et al. Diffuse large B-cell lymphoma with testicular involvement: outcome and risk of CNS relapse in the rituximab era. *Br J Haematol.* 2017;176(2):210-221.
97. Hosein PJ, Maragulia JC, Salzberg MP, et al. A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. *Br J Haematol.* 2014;165(3):358-363.
98. Klanova M, Sehn LH, Bence-Bruckler I, et al. Integration of cell of origin into the clinical CNS International Prognostic Index improves CNS relapse prediction in DLBCL. *Blood.* 2019;133(9):919-926.
99. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med.* 2018;24(5):679-690.
100. Schmitz R, Wright GW, Huang DW, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2018;378(15):1396-1407.
101. Savage KJ, Slack GW, Mottok A, et al. Impact of dual expression of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL. *Blood.* 2016;127(18):2182-2188.
102. Puckrin R, Darsa H, Ghosh S, Peters A, Stewart D. Lack of effectiveness of intravenous high-dose methotrexate for prevention of CNS relapse in patients with high-risk DLBCL: A retrospective analysis from Alberta, Canada. *Blood.* 2020;136(Supplement 1):26-27.
103. Tilly H, Lepage E, Coiffier B, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. *Blood.* 2003;102(13):4284-4289.
104. Cheah CY, Herbert KE, O'Rourke K, et al. A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. *Br J Cancer.* 2014;111(6):1072-1079.
105. Abramson JS, Hellmann M, Barnes JA, et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. *Cancer.* 2010;116(18):4283-4290.
106. Eyre TA, Djebbari F, Kirkwood AA, Collins GP. Efficacy of central nervous system prophylaxis with stand-alone intrathecal chemotherapy in diffuse large B-cell lymphoma patients treated with anthracycline-based chemotherapy in the rituximab era: a systematic review. *Haematologica.* 2020;105(7):1914-1924.
107. Wilson MR, Eyre TA, Martinez-Calle N, et al. Timing of high-dose methotrexate CNS prophylaxis in DLBCL: an analysis of toxicity and impact on R-CHOP delivery. *Blood Adv.* 2020;4(15):3586-3593.
108. Juweid ME SS, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, Wiseman GA, Kostakoglu L, Scheidhauer K, Buck A, Naumann R, Spaepen K, Hicks RJ, Weber WA, Reske SN, Schwaiger M, Schwartz LH, Zijlstra JM, Siegel BA, Cheson BD, Imaging Subcommittee of International Harmonization Project in Lymphoma Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol* 2007;25(5):571.
109. Larouche JF BF, Chassagne-Clément C, Ffrench M, Callet-Bauchu E, Sebban C, Ghesquières H, Broussais-Guillaumot F, Salles G, Coiffier B Lymphoma recurrence 5 years or later following diffuse large B-cell lymphoma: clinical characteristics and outcome. *J Clin Oncol* 2010;28(12):2094. .
110. Thompson CA GH, Maurer MJ, Cerhan JR, Biron P, Ansell SM, Chassagne-Clément C, Inwards DJ, Gargi T, Johnston PB, Nicolas-Virelizier E, Macon WR, Peix M, Micallef IN, Sebban C, Nowakowski GS, Porrata LF, Weiner GJ, Witzig TE, Habermann TM, Link BK Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. *J Clin Oncol* 2014 Nov;32(31):3506-12. Epub 2014 Sep 29. .

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111. El-Galaly TC MK, Bøgsted M, Brown P, Rossing M, Gang AO, Haglund A, Arboe B, Clausen MR, Jensen P, Pedersen M, Bukh A, Jensen BA, Poulsen CB, d'Amore F, Hutchings M Role of routine imaging in detecting recurrent lymphoma: A review of 258 patients with relapsed aggressive non-Hodgkin and Hodgkin lymphoma. *Am J Hematol* 2014;89(6):575. Epub 2014 Feb 24. .
112. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;333(23):1540-1545.
113. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. *J Clin Oncol.* 2017;35(5):544-551.
114. Chopra R, Goldstone AH, Pearce R, et al. Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: a case-controlled analysis of the European Bone Marrow Transplant Group Registry data. *J Clin Oncol.* 1992;10(11):1690-1695.
115. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol.* 2014;32(31):3490-3496.
116. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol.* 2010;28(27):4184-4190.
117. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol.* 2012;30(36):4462-4469.
118. Ng AK, Yahalom J, Goda JS, et al. Role of Radiation Therapy in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2018;100(3):652-669.
119. Chen YB, Lane AA, Logan B, et al. Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2015;21(6):1046-1053.
120. Dickinson M, Hoyt R, Roberts AW, et al. Improved survival for relapsed diffuse large B cell lymphoma is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy. *Br J Haematol.* 2010;150(1):39-45.
121. Filmont JE, Gisselbrecht C, Cuenca X, et al. The impact of pre- and post-transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation. *Cancer.* 2007;110(6):1361-1369.
122. Roland V, Bodet-Milin C, Moreau A, et al. Impact of high-dose chemotherapy followed by auto-SCT for positive interim [18F] FDG-PET diffuse large B-cell lymphoma patients. *Bone Marrow Transplant.* 2011;46(3):393-399.
123. Terasawa T, Dahabreh IJ, Nihashi T. Fluorine-18-fluorodeoxyglucose positron emission tomography in response assessment before high-dose chemotherapy for lymphoma: a systematic review and meta-analysis. *Oncologist.* 2010;15(7):750-759.
124. Vose JM, Zhang MJ, Rowlings PA, et al. Autologous transplantation for diffuse aggressive non-Hodgkin's lymphoma in patients never achieving remission: a report from the Autologous Blood and Marrow Transplant Registry. *J Clin Oncol.* 2001;19(2):406-413.
125. Thieblemont C CB. Lymphoma in older patients. *J Clin Oncol* 2007;25(14):1916. .
126. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.
127. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2019;380(1):45-56.

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128. Papageorgiou ES TP, Dimopoulos M, Pavlidis N, Fountzilas G, Papageorgiou S, Economopoulos T, Hellenic Cooperative Oncology Group. Combination chemotherapy with gemcitabine and vinorelbine in the treatment of relapsed or refractory diffuse large B-cell lymphoma: a phase-II trial by the Hellenic Cooperative Oncology Group. *Eur J Haematol* 2005;75(2):124. .
129. Moccia AA, F. Hitz, P. Hoskins. Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma. *Leuk Lymphoma.* 58(2):324-332.
130. Crump M, J. Kuruvilla, S. Couban,. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol.* 32(31):3490-3496.
131. Mounier N, T. El Gnaoui, H. Tilly,. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica.* 98(11):1726-1731.
132. Lopez A, A. Gutierrez, A. Palacios. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. *Eur J Haematol.* 80(2):127-132.
133. Chao NJ RS, Horning SJ CEPP(B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. *Blood* 1990;76(7):1293. .
134. Sehn LH HA, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, Assouline S, Kim TM, Kim WS, Ozcan M, Hirata J, Penuel E, Paulson JN, Cheng J, Ku G, Matasar MJ Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2020;38(2):155. Epub 2019 Nov 6. .
135. Ivanov V CD, Chetaille B, Esterni B, Olive D, Aurran-Schleinitz T, Schiano JM, Stoppa AM, Broussais-Guillaumot F, Blaise D, Bouabdallah R Efficacy and safety of lenalinomide combined with rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma. *Leuk Lymphoma* 2014 Nov;55(11):2508-13. Epub 2014 Mar 17. .
136. Vitolo U, Witzig TE, Gascoyne R, et al. ROBUST: First report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Hematol Oncol.* 2019;37(52):36-37.
137. Younes A, Sehn LH, Johnson P, et al. Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2019;37(15):1285-1295.
138. Davies A, Cummin TE, Barrans S, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2019;20(5):649-662.
139. NHMRC levels of evidence and grades for recommendations for developers of guidelines. In: Council NHaMR, ed. https://www.nhmrc.gov.au/sites/default/files/images/NHMRC%20Levels%20and%20Grades%20(2009).pdf2009.
140. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol.* 2014;32(27):3048-3058.
141. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v116-125.
142. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol.* 2016;174(1):43-56.

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143. Martin A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. *Haematologica.* 2008;93(12):1829-1836.
144. Pavlu J, Auner HW, Ellis S, et al. LACE-conditioned autologous stem cell transplantation for relapsed or refractory diffuse large B-cell lymphoma: treatment outcome and risk factor analysis from a single centre. *Hematol Oncol.* 2011;29(2):75-80.
145. Kebriaei P, Madden T, Kazerooni R, et al. Intravenous busulfan plus melphalan is a highly effective, well-tolerated preparative regimen for autologous stem cell transplantation in patients with advanced lymphoid malignancies. *Biol Blood Marrow Transplant.* 2011;17(3):412-420.

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TABLES AND FIGURES

Table and figure legend

TABLE 1: Recommended immunohistochemical testing of DLBCL

TABLE 2: Work-up and staging

ECOG: Eastern cooperative oncology group performance status. LDH: Lactate dehydrogenase. CNS: Central nervous system. CSF: Cerebral spinal fluid.

TABLE 3: Lugano classification of lymphoma staging

TABLE 4: International prognostic index (IPI) and subsequent variations

R-IPI: Revised-International Prognostic Index. NCCN National Comprehensive Cancer Network. LDH: Lactate dehydrogenase; ULN: Upper limit of normal; ECOG: Eastern cooperative oncology group performance status; CNS: Central nervous system; GI: gastrointestinal. OS: Overall survival

TABLE 5A: Lymphoma salvage chemotherapy regimens

AutoHCT: Autologous Haematopoietic Cell Transplant. R-GDP: Rituximab, gemcitabine, dexamethasone, cisplatin. R-ICE: Rituximab, ifosphamide, carboplatin, etoposide. R-DHAP: Rituximab, dexamethasone, cytarabine, cisplatin. R-ESHAP: Rituximab, etoposide, methylprednisolone, cytarabine, cisplatin.

TABLE 5B: Autologous transplant conditioning regimens

PFS: progression-free survival, OS: Overall survival. BEAM: Carmustine, etoposide, cytarabine, melphalan. LACE: Lomustine, cytarabine, cyclophosphamide, etoposide. BuMel: Busulphan, melphalan. BCNU: Carmustine.

FIGURE 1: Hans Classification of DLBCL phenotype

Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry

FIGURE 2: Relationship between Cell of Origin, antigen expression and chromosomal rearrangements.

GC-DLBCL: germinal centre-Diffuse Large B-Cell Lymphoma. non-GC-DLBCL-non-germinal-centre-DLBCL. DHL-Double hit lymphoma.

Table 1: Recommended immunohistochemical workup of DLBCL

Marker	% positive	Utility
CD20	>95%	Confirm B cell lineage, predicts sensitivity to Rituximab
PAX5	>95%	Confirm B cell lineage
CD10	30-50%	Suggests germinal centre subtype
MUM1	35-65%	Suggests post-germinal centre subtype (in absence of CD10)
BCL6	60-90%	Suggests germinal centre subtype (in absence of MUM1)
C-MYC	~30-40%	Confers inferior prognosis when expressed with BCL2
BCL2	~50-60%	Confers inferior prognosis when expressed with C-MYC
EBER-ISH	~5% in Western population	
CD5	5-10%	Defines CD5+ DLBCL
Ki67	Variable staining	Confirms high proliferation rate
CD30	10-20%	Common in anaplastic variant, prognostic relevance, therapeutic implications
Cyclin D1	0%	Excludes blastic mantle cell lymphoma

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Table 2. Work-up and staging

History	Presence of 'B' symptoms ECOG performance status History of immunosuppression Prior malignancy and chemotherapy (especially anthracycline) exposure
Physical examination	Involved nodal and extranodal sites Testicular examination in men
Blood tests[9,140-142]	FBE with film and flow cytometry to exclude circulating lymphoma Standard biochemistry (including calcium and phosphate), liver function, LDH, uric acid, beta-2 microglobulin, serum protein electrophoresis. Serology for HIV, Hepatitis B and C, EBV (plus PCR in cases of suspected immunosuppression-related DLBCL) Pregnancy test in women of child-bearing potential
Cardiac assessment	Transthoracic echocardiogram or gated heart pool scan for assessment of left ventricular ejection fraction
Imaging[9,140]	FDG-PET + CT (staged by Lugano classification, table 3) Contrast-enhanced CT in addition to FDG-PET in selected cases
CNS assessment[10]	MRI brain +/- spine and lumbar puncture for CSF cytology and flow cytometry in patients at risk of secondary CNS disease sufficient to justify prophylaxis (see CNS prophylaxis section)
Bone marrow aspirate and trephine[11]	FDG-PET has largely obviated the need for marrow assessment in DLBCL. It is still recommended in selected cases where the discovery of discordant marrow involvement would alter management

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Table 3. Lugano classification of lymphoma staging

Stage	Involvement	Extranodal status
Stage I (limited)	One node or group of adjacent nodes	Single extranodal lesion without nodal involvement
Stage II (limited)	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal with limited continguous extranodal involvement
Stage II bulky	As above with one lesion ≥7.5cm	
Stage III	Nodal disease above and below the diaphragm with spleen involvement	Not applicable
Stage IV	Additional non-contiguous extranodal involvement	Not applicable

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Table 4: International prognostic index and subsequent variations

Prognostic Factor	IPI	aaIPI (≤60yrs)	aaIPI (≤60yrs)	R-IPI	NCCN-IPI
Age (years)					
41to 60	0	0	0	0	1
61 to75	1	N/A	N/A	1	2
>75	1	N/A	N/A	1	3
Normalised serum LDH					
>1 to ≤3 x ULN	1	1	1	1	1
>3x ULN	1	1	1	1	2
ECOG ≥2	1	1	1	1	1
Stage III or IV	1	1	1	1	1
Specific Extranodal sites: bone marrow, CNS, Liver/GI tract or lung	0	0	0	0	1
Any extranodal disease (>1 total)	1	0	0	1	0
	Risk group				
	Low: 0-1 (5yr OS 73%) Low-intermediate: 2 (5yr OS 51%) High-intermediate: 3 (5yr OS 43%) High: 4-5 (5yr OS 26%)	Low: 0 (5yr OS 83%) Low-intermediate: 1 (5yr OS 69%) High-intermediate: 2 (5yr OS 46%) High: 3 (5yr OS 32%)	Low: 0 (5yr OS 83%) Low-intermediate: 1 (5yr OS 69%) High-intermediate: 2 (5yr OS 46%) High: 3 (5yr OS 32%)	Very good: 0 (4yr OS 94%) Good: 1-2 (4yr OS 79%) Poor: 3-5 (4yr OS 55%)	Low: 0-1 (5yr 96%) Low-intermediat 2-3 (5yr OS 82%) High-intermediat 4-5 (5yr OS 64%) High: ≥6 (5yr 33%)

LDH: Lactate dehydrogenase; ULN: Upper limit of normal; ECOG: Eastern cooperative oncology group performance status; CNS: Central nervous system; GI: gastrointestinal

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Table 5a. Lymphoma salvage regimens

Salvage regimens			
Regimen	Overall response rate	CR rate	% received autoHCT
R-GDP[130]	45%	13.5%	51%
R-ICE[116]	63%	36%	51%
R-DHAP[115,116]	44-64%	14-40%	49-55%
R-ESHAP[143]	67%	37%	62%

Table 5b. Autologous transplant regimens

AutoHCT conditioning regimens		
Regimen	PFS	OS
BEAM[119]	47% at 3 yrs	58% at 3 yrs
LACE[144]	42% at 5 years	47% at 5 years
BuMel[145]	64% at 2 years	67% at 2 years
Stanford BCNU[119]	39% at 3 yrs	43% at 3 yrs

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Figure 1: Hans Classification of DLBCL phenotype

Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray.

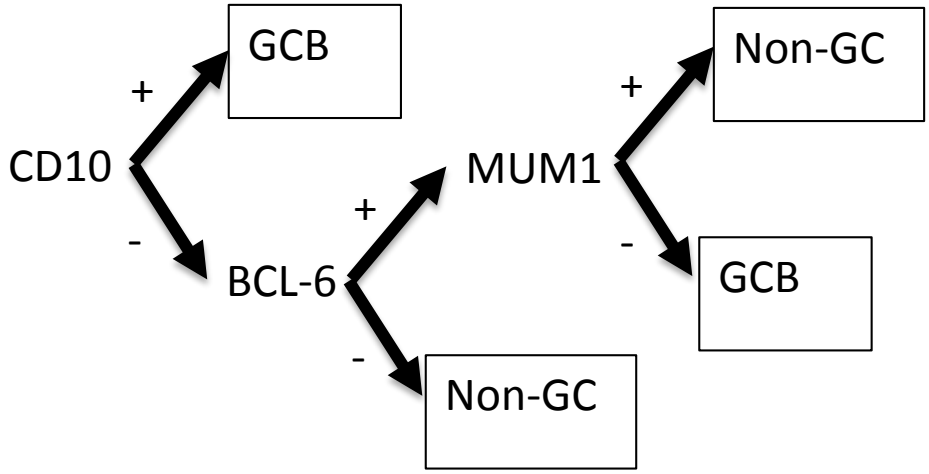

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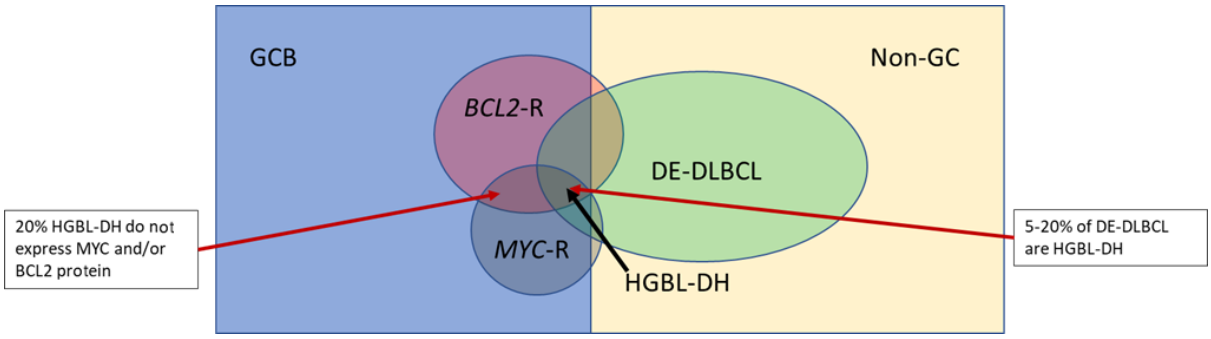
FIGURE 2: Relationship between Cell of Origin, antigen expression and chromosomal rearrangements.



GCB: germinal centre-Diffuse Large B-Cell Lymphoma. non-GC: non-germinal-centre-DLBCL. HGBL-DH: High-grade B cell lymphoma with rearrangements of MYC and/or BCL2 and BCL6.

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SUPPLEMENTARY MATERIAL

Metholodology

The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the NHMRC evidence hierarchy shown in Supplementary tables 1 and 2.[139] Statements without grading were considered justified standard clinical practice by the experts and the ALA members. The manuscript has been subjected to an anonymous peer review process.

SUPPLEMENTARY TABLE 1: Levels of Evidence

Level	Body of Evidence
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A trial with an independent blinded comparison with a valid reference standard
III-2	A comparative study with concurrent controls e.g. nonrandomised trial, cohort or case control study
III-3	A comparative study without concurrent controls, e.g. historical control study, or 2 or more single arm study
IV	Case series with post-test outcomes

*Adapted from NHMRC Evidence Hierarchy Table 2009

SUPPLEMENTARY TABLE 2: Grades of recommendations

Grade of Recommendation	Description
A	Body of evidence can be trusted to guide clinical practice
B	Body of evidence can be trusted to guide clinical practice in most situations
C	Body of evidence provides some support for recommendation(s), but care should be taken in its application

D	Body of evidence is weak, and recommendation must be applied with caution

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Diffuse large B-cell lymphoma: A consensus practice statement from the Australasian Lymphoma Alliance.

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoma subtype, accounting for 30-40% of lymphoma diagnoses. Though aggressive, cure is achievable in approximately 60% of cases with primary chemo-immunotherapy, and in a further substantial minority by salvage therapy and autologous stem cell transplantation. Despite promising activity in early phase clinical trials, no intensified or novel treatment regimen has improved outcomes over R-CHOP21 in randomised studies. However, there remain several areas of controversy including the most appropriate prognostic markers, CNS prophylaxis and the optimal treatment for patients with high-risk disease. This position statement presents an evidence-based synthesis of the literature for application in Australasian practice.

KEY WORDS

DLBCL, diagnosis, prognosis, management

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INTRODUCTION

Current controversies in DLBCL include identification of biomarkers for prognostication and treatment selection and management of specific risk groups such as limited stage disease, high-risk disease, and those at risk of central nervous system (CNS) dissemination. This practice statement provides healthcare professionals with an evidence-based approach to the investigation and management of DLBCL in the Australasian setting. Specific subtypes of extranodal disease are outside the scope of this statement.

METHODOLOGY

This Consensus Practice Statement was undertaken by a panel of lymphoma experts with particular interest in DLBCL under the auspices of the Australasian Lymphoma Alliance (ALA) in accordance with the ALA Consensus Practice Statement development policy (supplementary material).

INCIDENCE AND AETIOLOGY

The incidence of non-Hodgkin lymphoma (NHL) in Australia is approximately 20 cases per 100,000 person-years and is increasing, with DLBCL accounting for 30-40%.[1] Most patients are aged over 50 years at diagnosis with a slight male predominance. The aetiology is largely unclear, though immunosuppression and Epstein-Barr virus play a role in certain cases.[2]

DIAGNOSIS

Definitive diagnosis of DLBCL relies on biopsy. Excisional node biopsy is preferred, though core biopsy may be adequate in many cases.[3] Histologically, normal lymph node architecture is usually completely or partially effaced by a diffuse proliferation of large atypical lymphoid cells, which morphologically may be classified as centroblastic, immunoblastic or anaplastic.[4] Immunohistochemistry (IHC) and flow cytometry confirm the lineage of the neoplastic lymphoid cells. The neoplastic B cells are positive for B cell markers including CD20 which has therapeutic implications.[4] Other important IHC markers are shown in Table 1. The definitive final pathological classification of DLBCL, not otherwise specified (NOS) relies upon the exclusion of high-grade B cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements (HGBL-DH or HGBL-TH) by performing fluorescence in-situ hybridisation (FISH). Approximately 8% of cases resembling DLBCL morphologically are HGBL-DH when investigated for the presence of these gene rearrangements and the preferred approach is to test all cases.[5,6] If limited resources preclude routine FISH studies, testing only CD10 positive cases that concurrently express MYC and BCL2/BCL6 protein by IHC will capture most HGBL-DH whilst reducing the number of DLBCL proceeding to FISH.[6,7] Cases undergoing FISH may also utilise a stepwise approach by first testing *MYC* and, if present, subsequently testing for *BCL2* and *BCL6*. It is worth noting that FISH does not capture all cases with a HGBL-DH gene signature, which is prognostically relevant, though gene expression profiling is not routinely available.[8]

Recommendations:

- **Excisional lymph node biopsy is recommended for diagnosis, though core biopsy may be adequate in many cases. Fine needle aspiration is inadequate. (I, A)**
- **All biopsies should be reviewed by a histopathologist with lymphoma expertise (I, A)**
- **FISH for *MYC +/- BCL2 and BCL6* should ideally be performed on all cases, with rearrangement partner established where feasible (II, A)**

STAGING AND INITIAL WORK-UP

Thorough and expedient work-up of DLBCL is critical. Recommended work-up is in Table 2. Patients with highly symptomatic, bulky or clinically aggressive disease may require inpatient work-up to expedite delivery of chemotherapy. Pre-phase corticosteroids may also be required.

Recommendations:

- **Positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) combined with computed tomography (CT) is the staging modality of choice, with stage assigned by the Lugano classification (table 3) (I, A).[9]**
- **All cases should be discussed in a lymphoma multidisciplinary meeting (IV, A)**
- **MRI brain and spine and cerebrospinal fluid analysis is recommended for patients at high risk of CNS involvement (e.g. CNS-IPI ≥4, multiple extranodal sites; see CNS prophylaxis section) (III-2, A).[10]**
- **FDG-PET is adequate staging for concordant marrow involvement, though biopsy may identify discordant low-grade lymphoma and can be considered when this will alter management (I, B).[11]**
- **Counselling regarding contraception, menstrual management, pregnancy screening and fertility preservation should occur prior to administration of chemotherapy where clinically appropriate (IV, A).**

PROGNOSTIC FACTORS

IPI and clinical factors

Several prognostic tools discriminate DLBCL risk groups. The original International Prognostic Index (IPI) and the age-adjusted IPI (aaIPI)[12] were first described in the pre-rituximab era, but the same factors maintain prognostic significance in the rituximab era (revised-IPI).[13] The NCCN-IPI incorporates specific extranodal involvement, LDH and age to better stratify DLBCL risk when treated with R-CHOP (Table 4).[14]

Tumour bulk (≥7.5cm in maximal diameter) has been associated with poor prognosis in R-CHOP-treated patients.[15] Bone marrow, testicular, adrenal, renal, uterine involvement, primary breast DLBCL and high IPI are independently associated with higher CNS relapse risk.[16]

Molecular biology and biomarkers

Numerous pathobiological factors have been identified that add prognostic value to the IPI. The following have the most comprehensive data.

Cell of Origin (COO)

Gene expression profiling (GEP) identifies least three distinct molecular subtypes of DLBCL, arising at the various stages of differentiation. These are the germinal centre B-cell like (GCB), activated B-cell like (ABC) and an unclassifiable group.[17] When tested via GEP there is a clear and reproducible negative prognostic impact of the ABC subtype.[17,18]

The reported impact of IHC-assigned COO has been inconsistent, though probably retains some prognostic value.[19] The Hans algorithm (Figure 1) is most frequently used due to simplicity, availability and relative concordance with GEP.[20]

Protein expression

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The dual expression (DE) of MYC (≥40%) and BCL2 (≥50%) proteins by IHC has shown prognostic significance independent of the IPI and COO; indeed it has been suggested that DE-DLBCL accounts for the poor outcomes of ABC-type DLBCL where DE is more common.[17,21,22]

Chromosomal translocation

Single translocations involving solely *MYC, BCL2* or *BCL6* have not been consistently associated with prognosis. FISH studies showing *MYC* and *BCL2* and/or *BCL6* rearrangements define the entity HGBL-DH or HGBL-TH in the WHO 2016 classification and are generally associated with a poor prognosis.[4] However, the original retrospective studies suffered from selection bias, with unselected registry-based testing showing a more favourable outlook (5yr PFS ~58%, 5yr OS ~60%). The *MYC* translocation partner also appears of prognostic relevance, with translocations to an immunoglobulin gene (Ig) conferring the highest risk and a non-Ig partner conferring no additional risk; thus assessment of the break partner should be performed if feasible.[23]

Figure 2 demonstrates the relationship between COO, antigen overexpression and rearrangement of MYC and BCL2.[24]

Interim PET

Interim FDG-PET (iPET) has been assessed for its prognostic benefit and subsequent therapeutic implications. Although data are conflicting, most recent studies demonstrate a clear and independent association between iPET positivity and inferior outcomes.[25-29] The most robust prognostic measure appears to be the change in maximum standard uptake value (ΔSUVmax) after 4 cycles of R-CHOP; Deauville scores of 5 at this timepoint also predict refractory disease.[30,31] FDG-PET following two cycles also has prognostic importance and can predict early progression.[32] No randomised study has demonstrated a benefit of dose escalation based upon iPET and thus no recommendation for change in therapy based upon iPET can be made for routine clinical practice.[32,33] There is insufficient evidence to support de-escalation of therapy for early responders.

Recommendations:

- **The IPI should be recorded in all patients with DLBCL and the NCCN-IPI provides the best discrimination between prognostic groups (I, A).[34]**
- **COO should be determined in all cases of DLBCL and with specification of the method used (I, A).[4]**
- **All patients should have IHC for MYC and BCL2 (I, B)**
- **Interim FDG-PET adds prognostic value and may be performed following two or four cycles of R-CHOP (I, C)**
- **Primary therapy should be completed provided there has been at least a partial response on interim FDG-PET (I, B)**

TREATMENT

Primary chemo-immunotherapy

Standard treatment with chemo-immunotherapy results in OS rates of approximately 70%, 60%, and 45% at 3, 5, and 10 years respectively.[34]

All patients should receive rituximab in combination with chemotherapy given its addition confers a significant survival advantage with little additional toxicity.[35-39] The combination of rituximab with

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CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) is the standard regimen for most patients with DLBCL due to efficacy and tolerability.[40-44]

In unselected DLBCL, R-CHOP given every 21 days (R-CHOP21) showed equivalent efficacy with improved tolerability compared to a 14 day schedule (R-CHOP14) and remains the recommended front-line treatment.[45-47] For patients with advanced-stage disease, six cycles provides similar efficacy to eight.[39,48] There is no role for consolidation autologous stem cell transplantation (autoHCT) or maintenance therapy post R-CHOP for patients achieving complete metabolic response (CMR) due to absence of overall survival advantage.[49-53]

Recommendations:

- **6 cycles of R-CHOP21 is recommended for first-line advanced-stage DLBCL (I, A).**
- **Timely, full dose therapy should be delivered in patients <80 years of age where organ function and toxicity allow (III-1, A).[48]**
- **AutoHCT or maintenance therapy should not be used to consolidate DLBCL in complete metabolic remission following R-CHOP (I, A).**
- **For patients with limited stage, non-bulky (<7.5cm), IPI 0 disease 4 cycles of R-CHOP21 followed by 2 cycles of rituximab monotherapy is equivalent to 6 cycles (II, A).**

<u>Consolidation radiation therapy</u>

Radiation therapy (RT) is an effective locoregional consolidative therapy for DLBCL. Consolidation RT is most useful where risk of local relapse is the dominant site of failure, even after effective systemic therapy.

Primary indications for RT in first-line management of nodal DLBCL include (i) chemotherapy minimisation strategy in non-bulky limited-stage disease,[54,55] (ii) to consolidate sites at high risk of local relapse (e.g. bulky disease ≥7.5cm),[56,57] and (iii) to convert partial metabolic responses to complete response after initial chemoimmunotherapy.[58] Indications for RT in extra-nodal DLBCL sites are presented in other international guidelines.[59]

In general, doses of 30-36Gy are recommended to consolidate sites in CMR, delivered in 1.5-2Gy per fraction.[60,61] Doses of 36-50Gy may be required for FDG-PET-avid residual masses.[61]

Limited stage disease (non-bulky)

Conventional treatment approaches for non-bulky, limited stage disease include either (i) full course chemo-immunotherapy (6 cycles of R-CHOP),[56,62] or (ii) abbreviated chemo-immunotherapy (3-4 cycles of R-CHOP) with consolidation involved site RT (ISRT).[54,63,64] Where tolerated, full course chemo-immunotherapy is the preferred strategy for patients with higher risk disease, based on the continued pattern of late relapses observed following abbreviated systemic therapy in patients with stage-adjusted IPI ≥1.[63] However, for patients who may not tolerate full course chemo-immunotherapy, abbreviated chemo-immunotherapy and 30 Gy ISRT offers equivalent survival outcomes[63] with reduced chemo-toxicity and acceptable radiation-induced toxicity profile.[55,60,64,65]

For young (≤60 yrs) low-risk patients (aaIPI 0), four cycles of R-CHOP21 and two additional dose of rituximab without RT is non-inferior to 6 cycles of R-CHOP, with expected reduction in toxicity.[66] For patients >60 no other IPI risk factors, abbreviated chemotherapy without radiotherapy may also be a reasonable option in patients with a negative iPET, but this approach has not been subjected to a

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randomised study.[67] This approach is probably not suitable for patients with additional IPI risk factors where the preferred approach is six cycles of R-CHOP.[68]

Bulk

Several studies in the pre-FDG-PET era have demonstrated the benefit of consolidation RT to bulky or extranodal sites.[56,69] Omission of RT to original sites of bulk that achieve CMR by end of chemo-immunotherapy but have an incomplete CT response remains an area of controversy; the results of PET-adapted randomised studies are awaited (e.g. OPTIMAL>60, NCT01478542). Patients with bulky disease should not have systemic therapy abbreviated.

Recommendations:

- **ISRT is recommended over involved field RT due to equivalent efficacy and lower toxicity (I, A).[64]**
- **For patients with limited stage disease and stage-adjusted IPI ≥1, ISRT should be considered if it is necessary to abbreviate chemo-immunotherapy, e.g. for toxicity (II-B), though the preferred strategy remains 6 cycles of R-CHOP[54,63,70]**
- **ISRT remains standard of care for original sites of bulk (≥7.5cm) with incomplete CT resolution following R-CHOP (II,B), although omission of ISRT in PET-negative patients may be reasonable if toxicity is prohibitive (III-2,B).[71]**
- **ISRT is recommended to sites of incomplete metabolic response on FDG-PET unless other salvage is planned and if the disease is encompassable (III-2, A).**
- **For patients ≤60 with aaIPI=0, low-bulk, limited stage disease with CMR at chemo-immunotherapy completion, radiotherapy may be omitted (I,A).[66] A similar approach in patients >60yrs may be considered after a discussion of risks and benefits (III-2, C).[67]**

<u>Poor risk disease</u>

No randomised trial data supports using intensive regimens over R-CHOP21. However, such studies have not been powered to address patients with high clinical risk scores (e.g. aaIPI 2-3), so the question of whether intensified regimens improve outcomes for patients with both advanced-stage and high IPI disease has not been definitively answered.[45,46,72] R-CHOEP14 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) has shown relatively favourable outcomes in younger, high-risk patients but has not been compared with R-CHOP21 directly.[73]

The poor outcome of advanced-stage HGBL-DH, frequent association with other high risk clinical factors, and poor chance of salvage upon treatment failure has led to the widespread but speculative adoption of more intensive chemotherapy regimens such as R-DA-EPOCH and R-CHOEP14 with or without high dose autoHCT consolidation in first remission. Evidence for such approaches is limited to retrospective studies which suggest a higher CR rate following intensified induction, and which show no clear advantage to autoHCT in first complete response.[74,75]

Recommendations:

- **Patients with high biological risk should be enrolled in clinical trials where possible.**
- **No alteration of treatment strategy is recommended based on COO, DE or lone *MYC* rearrangement (I, A).**

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- **Intensification to R-DA-EPOCH or R-CHOEP14 in younger fit patienst with aaIPI 2-3 and in HGBL-DH may be justified in selected cases following discussion about the risks and benefits (III-2, C)**

Management of Elderly Patients with DLBCL

The potential for cure is reduced in the elderly due to increased likelihood of aggressive disease biology, medical comorbidities, functional decline and reduced tolerance of intensive chemotherapy.[76,77] There is no universally accepted definition of 'elderly' DLBCL patients in the literature. Until recently elderly patients with DLBCL were under-represented in clinical trials, thus the optimal treatment for these patients remains unclear.

For fit older patients <80yrs, six cycles of R-CHOP21 is suggested with supportive measures as listed below, and geriatric assessment tools may assist in determining fitness.[78] For patients >80yrs or those unfit for full dose R-CHOP21, R-mini-CHOP is a reasonable option with a reported 2-year OS and PFS of 59% and 47% respectively.[79] For unfit or frail patients regimens such as R-GCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisolone),[80] R-mini-CEOP (with epirubicin)[81] or R-CEEP (rituximab, cyclophosphamide, epirubicin, etoposide, prednisolone)[82] can be considered. R-CEOP (with etoposide) is an option for patients ineligible for an anthracycline.[83]

Recommendations:

- **The use of a geriatric assessment tool is recommended to guide treatment choice in elderly DLBCL patients (IV, C)**
- **Pre-phase prednisone is recommended in elderly patients (III-2, B).[84]**
- **Prophylactic G-CSF is recommended for all cycles of therapy (III, B).[85]**
- **Vitamin D supplementation should be considered in deficient patients (IV, C).[86-88]**
- **For fit older patients six cycles of R-CHOP21 is recommended with the above supportive measures (I,A).[78]**
- **For patients >80yrs or those unfit for R-CHOP21, R-mini-CHOP is a reasonable option (III-2, B)**
- **Abbreviated therapy (3-4 cycles of R-CHOP) plus ISRT can be considered in elderly patients with limited stage, non-bulky disease (II-B).**

Synchronous CNS/systemic disease

Patients presenting with synchronous CNS involvement at first presentation of systemic DLBCL have a poor prognosis driven largely by the CNS disease.[10] Some data support the use of AutoHCT in first complete remission, although the benefit is unclear if primary induction therapy includes high-dose methotrexate and cytarabine.[10,89] Recently published prospective trials taking an intensive induction approach with or without consolidative AutoSCT had relatively favourable outcomes in this group.[90,91] Intrathecal therapy can be added in those with leptomeningeal disease, and consolidation with radiotherapy and autoHCT at the discretion of the treating clinician is based upon disease response and patient factors.

Recommendations:

- **Patients with synchronous CNS and systemic DLBCL at diagnosis should receive a combination chemotherapy regimen that includes high-dose intravenous methotrexate and cytarabine as well as standard chemo-immunotherapy, which is**

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usually achieved with alternating treatment cycles. Consideration may be given to consolidation AutoHCT and RT (III-2, B).

CNS prophylaxis

Unselected DLBCL carries ~5% risk of CNS relapse and patients at high risk should be identified at diagnosis.[92] The most commonly used clinical risk score is the CNS-IPI which adds renal and adrenal involvement to the standard IPI factors to identify patients at high risk of CNS relapse.[93] However, a high-risk score (≥4) only identifies 55% of patients who will experience CNS relapse and we therefore also consider patients with >2 extranodal sites as high-risk.[94] Additional specific extranodal DLBCL sites appear to carry an independent CNS risk including testis, uterus and breast.[95-97] Certain biological features also appear to increase the risk of CNS presentations, including ABC subtype (particularly C5/MCD types),[98-100] DE-DLBCL and possibly HGBL-DH.[75,101]

The role of CNS prophylaxis is controversial with conflicting data and forthcoming randomised clinical trials are unlikely due to the relative infrequency of events. Recent retrospective analyses casts doubt on the benefit of intravenous methotrexate prophylaxis, though were likely underpowered.[102] Intensive systemic regimens with inbuilt CNS-penetrating agents and the administration of high-dose intravenous methotrexate appear to lower the risk of CNS progression; the latter with less associated toxicity.[103-105]

Recommendations:

- **Intrathecal methotrexate prophylaxis is not recommended unless systemic prophylaxis is not deliverable (III-2, B).[104,106]**
- **2-3 cycles of high-dose intravenous methotrexate (e.g. 3g/m^2) in addition to R-CHOP21 is reasonable in patients with high CNS-IPI and those with multiple or specific extranodal sites (III-2, C).[104,105]**
- **CNS prophylaxis in patients with high biological risk DLBCL but low- or intermediate-risk CNS-IPI scores should be discussed on a case-by-case basis.**
- **CNS-penetrant therapy may be delivered at the completion of or intercalated with R-CHOP, , though an intercalated approach may increase toxicity and compromise R-CHOP delivery.[107]**

RESPONSE ASSESSMENTA ND FOLLOW UP

Following completion of induction chemo-immunotherapy, patients should be re-evaluated to confirm disease response. The EOT imaging modality of choice is FDG-PET/CT, which may also be helpful in guiding RT dose prescription and planning.[108]

Upon achieving CMR, conventional practice is for 5 years of follow up for monitoring of complications of therapy and disease relapse.[109] Surveillance imaging for relapse detection is low yield and confers no survival advantage compared with clinically detected relapse. Therefore, the current surveillance strategy centres on clinical and laboratory findings, with imaging indicated only when there is clinical suspicion of relapse. Interval FDG-PET may be employed in cases where the EOT FDG-PET is equivocal.

Recommendations:

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- **EOT FDG-PET/CT should be performed at least 3 weeks, and preferably 6-8 weeks after completion of chemo-immunotherapy, and 8-12 weeks after the completion of RT.[108]**
- **We recommend defining complete metabolic remission in accordance with the Lugano classification (I, A).[9]**
- **Imaging for the detection of relapse should be performed due to clinical suspicion rather than surveillance (III-2, B).[110,111]**

RELAPSED/REFRACTORY (R/R) DLBCL: TRANSPLANT ELIGIBLE PATIENTS

In transplant-eligible patients experiencing first relapse/progression, salvage chemo-immunotherapy followed by autoHCT provides a survival benefit over salvage therapy alone.[112] Disease response as determined by FDG-PET is the most critical factor in proceeding to autoHCT, and depth of response pre-transplant correlates with post-transplant outcomes.[113] There is no routine role for allogeneic transplantation in second complete remission.[114]

The commonly used salvage and autoHCT conditioning regimens are summarised in table 5a and 5b though there are currently insufficient data to recommend one over another. The only two randomised studies failed to show a difference in response or survival for R-ICE vs R-DHAP and R-DHAP vs R-GDP respectively, though R-DHAP appears more toxic.[115,116] Additionally, ofatumumab offered no benefit over Rituximab with a DHAP backbone.[113] There is no benefit to rituximab maintenance following autoHCT.[117]

Radiotherapy before or after autoHCT to consolidate responses should be decided on a case-by-case basis, typically where all sites of disease can be addressed within a radiation field. Guidelines were recently published by ILROG.[118]

Myeloablative conditioning regimens for autologous HCT have not been directly compared in prospective trials. BEAM is the most commonly used regimen.[119]

Recommendations:

- **In patients experiencing first relapse/progression who are eligible for high-dose chemotherapy with autoHCT, we recommend salvage chemo-immunotherapy followed by autoHCT (I, A)**

- **Sensitivity to salvage chemo-immunotherapy as determined by FDG-PET is a prerequisite to proceeding to autoHCT due to high failure rates with chemoresistance (III-2, A).[120-124]**

- **Consideration should be given to alternative or additional salvage strategies for responding patients failing to achieve CR by FDG-PET prior to autoSCT. Options including proceeding to AutoSCT, radiotherapy, CAR-T cells and clinical trial should be decided on a case-by-case basis (III-2, C).**

R/R DLBCL: TRANSPLANT INELIGIBLE PATIENTS

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The management of R/R DLBCL in transplant ineligible patients is often non-curative, though a proportion of patients with refractory disease encompassable in a single RT field may be cured by this approach.[125] For the remainder, there is no standard approach, and thus we recommend early consideration of active clinical trials where available. Chimeric Antigen Receptor T cell therapy (CAR-T) beyond second-line treatment can offer durable remissions and probably cure in 30-40% of treated patients. CAR-T are approved in Australia in patients who have relapsed or who are refractory to at least 2 lines of systemic treatment, and who have relapsed or are ineligible for a transplant. However, the complexity of the procedure precludes its use in many patients, especially those with refractory lymphoma or medical comorbidities.[126,127] Whilst an in-depth discussion of this topic falls outside the scope of this manuscript, it is recommended that an early discussion with a CAR-T centre should be considered where clinically appropriate.

For many patients, a potentially curative option is unavailable, and the goal of therapy is disease control and quality of life, thus more intensive salvage regimens are usually inappropriate. Gemcitabine-based regimens offer a reasonable combination of efficacy and tolerability.[128-133] Novel agents such as polatuzumab-vedotin with bendamustine and lenalidomide may provide additional options in selected cases, pending regulatory approval/reimbursement in Australia.[134,135] Radiotherapy and high-dose corticosteroid may provide symptom palliation. Higher dose RT may achieve durable remissions in the uncommon circumstance of localised R/R DLBCL.[59]

Recommendations:

- **We recommend enrolment in clinical trials as the first option where available for transplant ineligible R/R DLBCL patients**
- **CAR-T therapy provides a potentially curative option for some patients and early discussion with a CAR-T center is recommended if this approach is considered.**
- **RT should be considered for patients with limited-stage relapse**

FUTURE DIRECTIONS AND RESEARCH PRIORITIES

An immense amount of research has been conducted in DLBCL since the introduction of rituximab without significant improvement in outcomes. Several studies have investigated the addition of novel agents to patients with poor biological risk tumours without a survival advantage.[136-138] As our understanding of the genetic and functional drivers of DLBCL increases, clinical trial design needs to evolve to address not only those patients with poor prognostic disease, but rational drug combinations that target pathogenic mechanisms.

Antibody-drug conjugates such as polatuzumab-vedotin clearly have activity in relapsed and refractory disease and are currently being investigated in the up-front setting (NCT03274492). While CAR-T therapy is approved in the third line-setting, ongoing trials are actively exploring their role in high-risk first relapse in the transplant-eligible population. Bispecific T-cell engaging antibodies also show significant promise in chemo-refractory disease.

Improving access to treatment for certain subgroups such those from regional and remote areas remains a challenge and the use of telehealth and teletrials technology may improve the disparate outcomes for these patients.

Methodology

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These consensus practice statements were developed in accordance with the Australasian Lymphoma Alliance (ALA) policy for Consensus Practice Statement development. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the NHMRC evidence hierarchy shown in tables 6 and 7.[139] Statements without grading were considered justified standard clinical practice by the experts and the ALA members. The manuscript has been subjected to an anonymous peer review process.

References

1. Bufton B, Kilo R, Wong H, H. R, Harvey J, Moon L. *Cancer in Australia.* Australian Institute of Health and Wellbeing2019.
2. Dharnidharka VR, Webster AC, Martinez OM, Preiksaitis JK, Leblond V, Choquet S. Post-transplant lymphoproliferative disorders. *Nat Rev Dis Primers.* 2016;2:15088.
3. Johl A, Lengfelder E, Hiddemann W, Klapper W, German Low-grade Lymphoma Study G. Core needle biopsies and surgical excision biopsies in the diagnosis of lymphoma-experience at the Lymph Node Registry Kiel. *Ann Hematol.* 2016;95(8):1281-1286.
4. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood.* 2016;127(20):2375-2390.
5. Pedersen MO, Gang AO, Poulsen TS, et al. Double-hit BCL2/MYC translocations in a consecutive cohort of patients with large B-cell lymphoma - a single centre's experience. *Eur J Haematol.* 2012;89(1):63-71.
6. Scott DW, King RL, Staiger AM, et al. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with diffuse large B-cell lymphoma morphology. *Blood.* 2018;131(18):2060-2064.
7. Merron B, Davies A. Double hit lymphoma: How do we define it and how do we treat it? *Best Pract Res Clin Haematol.* 2018;31(3):233-240.
8. Ennishi D, Jiang A, Boyle M, et al. Double-Hit Gene Expression Signature Defines a Distinct Subgroup of Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2019;37(3):190-201.
9. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol.* 2014;32(27):3059-3068.
10. Wight JC, Yue M, Keane C, et al. Outcomes of synchronous systemic and central nervous system (CNS) involvement of diffuse large B-cell lymphoma are dictated by the CNS disease: a collaborative study of the Australasian Lymphoma Alliance. *Br J Haematol.* 2019;187(2):174-184.
11. Khan AB, Barrington SF, Mikhaeel NG, et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. *Blood.* 2013;122(1):61-67.
12. Shipp MA, Harrington DP. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. *N Engl J Med.* 1993;329(14):987-994.
13. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood.* 2007;109(5):1857-1861.
14. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood.* 2014;123(6):837-842.
15. Pfreundschuh M, Ho AD, Cavallin-Stahl E, et al. Prognostic significance of maximum tumour (bulk) diameter in young patients with good-prognosis diffuse large-B-cell lymphoma treated

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with CHOP-like chemotherapy with or without rituximab: an exploratory analysis of the MabThera International Trial Group (MInT) study. *Lancet Oncol.* 2008;9(5):435-444.
16. Fletcher CD, Kahl BS. Central nervous system involvement in diffuse large B-cell lymphoma: an analysis of risks and prevention strategies in the post-rituximab era. *Leuk Lymphoma.* 2014;55(10):2228-2240.
17. Scott DW, Mottok A, Ennishi D, et al. Prognostic Significance of Diffuse Large B-Cell Lymphoma Cell of Origin Determined by Digital Gene Expression in Formalin-Fixed Paraffin-Embedded Tissue Biopsies. *J Clin Oncol.* 2015;33(26):2848-2856.
18. Vitolo U, Trneny M, Belada D, et al. Obinutuzumab or Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Previously Untreated Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2017;35(31):3529-3537.
19. Read JA, Koff JL, Nastoupil LJ, Williams JN, Cohen JB, Flowers CR. Evaluating cell-of-origin subtype methods for predicting diffuse large B-cell lymphoma survival: a meta-analysis of gene expression profiling and immunohistochemistry algorithms. *Clin Lymphoma Myeloma Leuk.* 2014;14(6):460-467 e462.
20. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004;103(1):275-282.
21. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol.* 2012;30(28):3452-3459.
22. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood.* 2013;121(20):4021-4031.
23. Rosenwald A, Bens S, Advani R, et al. Prognostic Significance of MYC Rearrangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium. *J Clin Oncol.* 2019;37(35):3359-3368.
24. Wight JC, Chong G, Grigg AP, Hawkes EA. Prognostication of diffuse large B-cell lymphoma in the molecular era: moving beyond the IPI. *Blood Rev.* 2018;32(5):400-415.
25. Yang DH, Ahn JS, Byun BH, et al. Interim PET/CT-based prognostic model for the treatment of diffuse large B cell lymphoma in the post-rituximab era. *Ann Hematol.* 2013;92(4):471-479.
26. Wu X, Pertovaara H, Korkola P, et al. Early interim PET/CT predicts post-treatment response in diffuse large B-cell lymphoma. *Acta Oncol.* 2014;53(8):1093-1099.
27. Nols N, Mounier N, Bouazza S, et al. Quantitative and qualitative analysis of metabolic response at interim positron emission tomography scan combined with International Prognostic Index is highly predictive of outcome in diffuse large B-cell lymphoma. *Leuk Lymphoma.* 2014;55(4):773-780.
28. Pardal E, Coronado M, Martin A, et al. Intensification treatment based on early FDG-PET in patients with high-risk diffuse large B-cell lymphoma: a phase II GELTAMO trial. *Br J Haematol.* 2014;167(3):327-336.
29. Lanic H, Mareschal S, Mechken F, et al. Interim positron emission tomography scan associated with international prognostic index and germinal center B cell-like signature as prognostic index in diffuse large B-cell lymphoma. *Leuk Lymphoma.* 2012;53(1):34-42.
30. Hertzberg M. High-risk DLBCL: interim PET? Not yet. *Blood.* 2017;130(11):1277-1278.
31. Hertzberg M, Gandhi MK, Trotman J, et al. Early treatment intensification with R-ICE and 90Y-ibritumomab tiuxetan (Zevalin)-BEAM stem cell transplantation in patients with high-risk diffuse large B-cell lymphoma patients and positive interim PET after 4 cycles of R-CHOP-14. *Haematologica.* 2017;102(2):356-363.

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32. Duhrsen U, Muller S, Hertenstein B, et al. Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas (PETAL): A Multicenter, Randomized Phase III Trial. *J Clin Oncol.* 2018;36(20):2024-2034.
33. Casasnovas RO, Ysebaert L, Thieblemont C, et al. FDG-PET-driven consolidation strategy in diffuse large B-cell lymphoma: final results of a randomized phase 2 study. *Blood.* 2017;130(11):1315-1326.
34. Ruppert AS, Dixon JG, Salles G, et al. International prognostic indices in diffuse large B-cell lymphoma: a comparison of IPI, R-IPI, and NCCN-IPI. *Blood.* 2020;135(23):2041-2048.
35. Coiffier B, Thieblemont C, Van Den Neste E, et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. *Blood.* 2010;116(12):2040-2045.
36. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 2005;23(18):4117-4126.
37. Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. *J Clin Oncol.* 2006;24(19):3121-3127.
38. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2011;12(11):1013-1022.
39. Pfreundschuh M, Schubert J, Ziepert M, et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol.* 2008;9(2):105-116.
40. Bartlett NL, Petroni GR, Parker BA, et al. Dose-escalated cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (CHOPE) chemotherapy for patients with diffuse lymphoma: Cancer and Leukemia Group B studies 8852 and 8854. *Cancer.* 2001;92(2):207-217.
41. Björkholm M, Andersson T, Ahlbom A, Ösby E. CNOP (mitoxantrone) chemotherapy is inferior to CHOP (doxorubicin) in the treatment of patients with aggressive non-Hodgkin lymphoma (meta-analysis). *Eur J Haematol.* 2008;80(6):477-482.
42. Burton C, Smith P, Vaughan-Hudson G, et al. Comparison of CHOP versus CIOP in good prognosis younger patients with histologically aggressive non-Hodgkin lymphoma. *Br J Haematol.* 2005;130(4):536-541.
43. Gaynor ER, Unger JM, Miller TP, et al. Infusional CHOP chemotherapy (CVAD) with or without chemosensitizers offers no advantage over standard CHOP therapy in the treatment of lymphoma: a Southwest Oncology Group Study. *J Clin Oncol.* 2001;19(3):750-755.
44. Sparano JA, Weller E, Nazeer T, et al. Phase 2 trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with poor-prognosis, intermediate-grade non-Hodgkin lymphoma: an Eastern Cooperative Oncology Group trial (E3493). *Blood.* 2002;100(5):1634-1640.
45. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet.* 2013;381(9880):1817-1826.
46. Delarue R, Tilly H, Mounier N, et al. Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial. *Lancet Oncol.* 2013;14(6):525-533.

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47. Kamel S, O'Connor S, Lee N, Filshie R, Nandurkar H, Tam CS. High incidence of Pneumocystis jirovecii pneumonia in patients receiving biweekly rituximab and cyclophosphamide, adriamycin, vincristine, and prednisone. *Leuk Lymphoma.* 2010;51(5):797-801.
48. Marangolo M, Bengala C, Conte PF, et al. Dose and outcome: the hurdle of neutropenia (Review). *Oncol Rep.* 2006;16(2):233-248.
49. Cortelazzo S, Tarella C, Gianni AM, et al. Randomized Trial Comparing R-CHOP Versus High-Dose Sequential Chemotherapy in High-Risk Patients With Diffuse Large B-Cell Lymphomas. *J Clin Oncol.* 2016;34(33):4015-4022.
50. Epperla N, Hamadani M, Reljic T, Kharfan-Dabaja MA, Savani BN, Kumar A. Upfront autologous hematopoietic stem cell transplantation consolidation for patients with aggressive B-cell lymphomas in first remission in the rituximab era: A systematic review and meta-analysis. *Cancer.* 2019;125(24):4417-4425.
51. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 2013;369(18):1681-1690.
52. Morrison VA, Weller EA, Habermann TM, et al. Maintenance rituximab (MR) compared to observation (OBS) after R-CHOP or CHOP in older patients (pts) with diffuse large B-cell lymphoma (DLBCL): An Intergroup E4494/C9793 update. *J Clin Oncol.* 2007;25(18_suppl):8011-8011.
53. Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide Maintenance Compared With Placebo in Responding Elderly Patients With Diffuse Large B-Cell Lymphoma Treated With First-Line Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. *J Clin Oncol.* 2017;35(22):2473-2481.
54. Persky DO, Unger JM, Spier CM, et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. *J Clin Oncol.* 2008;26(14):2258-2263.
55. Miller TP, Dahlberg S, Cassady JR, et al. Chemotherapy Alone Compared with Chemotherapy plus Radiotherapy for Localized Intermediate- and High-Grade Non-Hodgkin's Lymphoma. *N Engl J Med.* 1998;339(1):21-26.
56. Pfreundschuh M, Murawski N, Ziepert M, et al. Radiotherapy (RT) to bulky (B) and extralymphatic (E) disease in combination with 6xR-CHOP-14 or R-CHOP-21 in young good-prognosis DLBCL patients: Results of the 2x2 randomized UNFOLDER trial of the DSHNHL/GLA. *J Clin Oncol.* 2018;36(15_suppl):7574-7574.
57. Held G, Murawski N, Ziepert M, et al. Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. *J Clin Oncol.* 2014;32(11):1112-1118.
58. Dabaja BS, Hess K, Shihadeh F, et al. Positron Emission Tomography/Computed Tomography Findings During Therapy Predict Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Chemotherapy Alone but Not in Those Who Receive Consolidation Radiation. *Int J Radiat Oncol Biol Phys.* 2014;89(2):384-391.
59. Yahalom J, Illidge T, Specht L, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2015;92(1):11-31.
60. Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial. *Radiother Oncol.* 2011;100(1):86-92.
61. Wirth A, Mikhaeel NG, Aleman BMP, et al. Involved Site Radiation Therapy in Adult Lymphomas: An Overview of International Lymphoma Radiation Oncology Group Guidelines. *Int J Radiat Oncol Biol Phys.* 2020;107(5):909-933.
62. Pfreundschuh M, Kuhnt E, Trümper L, et al. Randomised Intergroup Trial of First line Treatment for young Low-Risk Patients (<61 years) with Diffuse Large B-Cell Non-Hodgkin's Lymphoma (DLBCL) with a CHOP-like Regimen with or without the Anti-CD20 Antibody Rituximab – 6-Year Follow-up of the Mint Study of the Mabthera International Trial (MInT) Group. *Blood.* 2010;116(21):111-111.

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63. Stephens DM, Li H, LeBlanc ML, et al. Continued Risk of Relapse Independent of Treatment Modality in Limited-Stage Diffuse Large B-Cell Lymphoma: Final and Long-Term Analysis of Southwest Oncology Group Study S8736. *J Clin Oncol.* 2016;34(25):2997-3004.
64. Campbell BA, Connors JM, Gascoyne RD, Morris WJ, Pickles T, Sehn LH. Limited-stage diffuse large B-cell lymphoma treated with abbreviated systemic therapy and consolidation radiotherapy. *Cancer.* 2012;118(17):4156-4165.
65. Pugh TJ, Ballonoff A, Rusthoven KE, et al. Cardiac mortality in patients with stage I and II diffuse large B-cell lymphoma treated with and without radiation: a surveillance, epidemiology, and end-results analysis. *Int J Radiat Oncol Biol Phys.* 2010;76(3):845-849.
66. Poeschel V, Held G, Ziepert M, et al. Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial. *Lancet.* 2019;394(10216):2271-2281.
67. Persky DO, Li H, Stephens DM, et al. PET-Directed Therapy for Patients with Limited-Stage Diffuse Large B-Cell Lymphoma - Results of Intergroup Nctn Study S1001. *Blood.* 2019;134(Supplement_1):349-349.
68. Hawkes EA, Opat S, Hertzberg M. Caution in Expanding the Use of Abbreviated R-CHOP to Poor-Risk Limited-Stage DLBCL. *J Clin Oncol.* 2020;38(35):4221-4222.
69. Held G, Murawski N, Ziepert M, et al. Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma. *J Clin Oncol.* 2014;32(11):1112-1118.
70. Odejide OO, Cronin AM, Davidoff AJ, LaCasce AS, Abel GA. Limited stage diffuse large B-cell lymphoma: comparative effectiveness of treatment strategies in a large cohort of elderly patients. *Leuk Lymphoma.* 2015;56(3):716-724.
71. Freeman CL, Savage KJ, Villa D, et al. Long-Term Results of PET-Guided Radiation in Advanced-Stage Diffuse Large B-Cell Lymphoma Patients Treated with R-CHOP. *Blood.* 2020.
72. Bartlett NL, Wilson WH, Jung SH, et al. Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. *J Clin Oncol.* 2019;37(21):1790-1799.
73. Schmitz N, Nickelsen M, Ziepert M, et al. Conventional chemotherapy (CHOEP-14) with rituximab or high-dose chemotherapy (MegaCHOEP) with rituximab for young, high-risk patients with aggressive B-cell lymphoma: an open-label, randomised, phase 3 trial (DSHNHL 2002-1). *Lancet Oncol.* 2012;13(12):1250-1259.
74. Landsburg DJ, Falkiewicz MK, Maly J, et al. Outcomes of Patients With Double-Hit Lymphoma Who Achieve First Complete Remission. *J Clin Oncol.* 2017;35(20):2260-2267.
75. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood.* 2014;124(15):2354-2361.
76. d'Amore F, Brincker H, Christensen BE, et al. Non-Hodgkin's lymphoma in the elderly. A study of 602 patients aged 70 or older from a Danish population-based registry. The Danish LYEO-Study Group. *Ann Oncol.* 1992;3(5):379-386.
77. Nabhan C, Smith SM, Helenowski I, et al. Analysis of very elderly (>/=80 years) non-hodgkin lymphoma: impact of functional status and co-morbidities on outcome. *Br J Haematol.* 2012;156(2):196-204.
78. Beygi S, Sadashiv S, Reilly JB, Khan C, Lister J. Frontline treatment of diffuse large B-cell lymphoma in elderly: a systematic review of clinical trials in post-rituximab era. *Leuk Lymphoma.* 2018;59(12):2847-2861.
79. Peyrade F, Jardin F, Thieblemont C, et al. Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial. *Lancet Oncol.* 2011;12(5):460-468.
80. Fields PA, Townsend W, Webb A, et al. De novo treatment of diffuse large B-cell lymphoma with rituximab, cyclophosphamide, vincristine, gemcitabine, and prednisolone in patients

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with cardiac comorbidity: a United Kingdom National Cancer Research Institute trial. *J Clin Oncol.* 2014;32(4):282-287.
81. Merli F, Luminari S, Rossi G, et al. Cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab versus epirubicin, cyclophosphamide, vinblastine, prednisone and rituximab for the initial treatment of elderly "fit" patients with diffuse large B-cell lymphoma: results from the ANZINTER3 trial of the Intergruppo Italiano Linfomi. *Leuk Lymphoma.* 2012;53(4):581-588.
82. Yeung J, Campbell A, Bryant C, et al. Safety and Efficacy of R-CEEP (Rituximab, Cyclophosphamide, Epirubicin, Etoposide, Prednisolone) in Elderly or Unfit Patients with Diffuse Large B-Cell Lymphoma (DLBCL): A Retrospective Single-Centre Experience. *Blood.* 2019;134(Supplement 1):2911.
83. Rashidi A, Oak E, Carson KR, Wagner-Johnston ND, Kreisel F, Bartlett NL. Outcomes with R-CEOP for R-CHOP-ineligible patients with diffuse large B-cell lymphoma are highly dependent on cell of origin defined by Hans criteria. *Leuk Lymphoma.* 2016;57(5):1191-1193.
84. Pfreundschuh M. How I treat elderly patients with diffuse large B-cell lymphoma. *Blood.* 2010;116(24):5103-5110.
85. Repetto L, Biganzoli L, Koehne CH, et al. EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. *Eur J Cancer.* 2003;39(16):2264-2272.
86. Bittenbring JT, Neumann F, Altmann B, et al. Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. *J Clin Oncol.* 2014;32(29):3242-3248.
87. Drake MT, Maurer MJ, Link BK, et al. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. *J Clin Oncol.* 2010;28(27):4191-4198.
88. Hohaus S, Tisi MC, Bellesi S, et al. Vitamin D deficiency and supplementation in patients with aggressive B-cell lymphomas treated with immunochemotherapy. *Cancer Med.* 2018;7(1):270-281.
89. Damaj G, Ivanoff S, Coso D, et al. Concomitant systemic and central nervous system non-Hodgkin lymphoma: the role of consolidation in terms of high dose therapy and autologous stem cell transplantation. A 60-case retrospective study from LYSA and the LOC network. *Haematologica.* 2015;100(9):1199-1206.
90. Ferreri AJM, Doorduijn JK, Re A, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. *Lancet Haematol.* 2021;8(2):e110-e121.
91. McMillan AK, Phillips EH, Kirkwood AA, et al. Favourable outcomes for high-risk diffuse large B-cell lymphoma (IPI 3-5) treated with front-line R-CODOX-M/R-IVAC chemotherapy: results of a phase 2 UK NCRI trial. *Ann Oncol.* 2020;31(9):1251-1259.
92. Ghose A, Elias HK, Guha G, Yellu M, Kundu R, Latif T. Influence of Rituximab on Central Nervous System Relapse in Diffuse Large B-Cell Lymphoma and Role of Prophylaxis--A Systematic Review of Prospective Studies. *Clin Lymphoma Myeloma Leuk.* 2015;15(8):451-457.
93. Schmitz N, Zeynalova S, Nickelsen M, et al. CNS International Prognostic Index: A Risk Model for CNS Relapse in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP. *J Clin Oncol.* 2016;34(26):3150-3156.
94. El-Galaly TC, Villa D, Michaelsen TY, et al. The number of extranodal sites assessed by PET/CT scan is a powerful predictor of CNS relapse for patients with diffuse large B-cell lymphoma: An international multicenter study of 1532 patients treated with chemoimmunotherapy. *Eur J Cancer.* 2017;75:195-203.
95. El-Galaly TC, Cheah CY, Hutchings M, et al. Uterine, but not ovarian, female reproductive organ involvement at presentation by diffuse large B-cell lymphoma is associated with poor

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outcomes and a high frequency of secondary CNS involvement. *Br J Haematol.* 2016;175(5):876-883.
96. Kridel R, Telio D, Villa D, et al. Diffuse large B-cell lymphoma with testicular involvement: outcome and risk of CNS relapse in the rituximab era. *Br J Haematol.* 2017;176(2):210-221.
97. Hosein PJ, Maragulia JC, Salzberg MP, et al. A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. *Br J Haematol.* 2014;165(3):358-363.
98. Klanova M, Sehn LH, Bence-Bruckler I, et al. Integration of cell of origin into the clinical CNS International Prognostic Index improves CNS relapse prediction in DLBCL. *Blood.* 2019;133(9):919-926.
99. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med.* 2018;24(5):679-690.
100. Schmitz R, Wright GW, Huang DW, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2018;378(15):1396-1407.
101. Savage KJ, Slack GW, Mottok A, et al. Impact of dual expression of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL. *Blood.* 2016;127(18):2182-2188.
102. Puckrin R, Darsa H, Ghosh S, Peters A, Stewart D. Lack of effectiveness of intravenous high-dose methotrexate for prevention of CNS relapse in patients with high-risk DLBCL: A retrospective analysis from Alberta, Canada. *Blood.* 2020;136(Supplement 1):26-27.
103. Tilly H, Lepage E, Coiffier B, et al. Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. *Blood.* 2003;102(13):4284-4289.
104. Cheah CY, Herbert KE, O'Rourke K, et al. A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. *Br J Cancer.* 2014;111(6):1072-1079.
105. Abramson JS, Hellmann M, Barnes JA, et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. *Cancer.* 2010;116(18):4283-4290.
106. Eyre TA, Djebbari F, Kirkwood AA, Collins GP. Efficacy of central nervous system prophylaxis with stand-alone intrathecal chemotherapy in diffuse large B-cell lymphoma patients treated with anthracycline-based chemotherapy in the rituximab era: a systematic review. *Haematologica.* 2020;105(7):1914-1924.
107. Wilson MR, Eyre TA, Martinez-Calle N, et al. Timing of high-dose methotrexate CNS prophylaxis in DLBCL: an analysis of toxicity and impact on R-CHOP delivery. *Blood Adv.* 2020;4(15):3586-3593.
108. Juweid ME SS, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, Wiseman GA, Kostakoglu L, Scheidhauer K, Buck A, Naumann R, Spaepen K, Hicks RJ, Weber WA, Reske SN, Schwaiger M, Schwartz LH, Zijlstra JM, Siegel BA, Cheson BD, Imaging Subcommittee of International Harmonization Project in Lymphoma Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *J Clin Oncol* 2007;25(5):571.
109. Larouche JF BF, Chassagne-Clément C, Ffrench M, Callet-Bauchu E, Sebban C, Ghesquières H, Broussais-Guillaumot F, Salles G, Coiffier B Lymphoma recurrence 5 years or later following diffuse large B-cell lymphoma: clinical characteristics and outcome. *J Clin Oncol* 2010;28(12):2094. .
110. Thompson CA GH, Maurer MJ, Cerhan JR, Biron P, Ansell SM, Chassagne-Clément C, Inwards DJ, Gargi T, Johnston PB, Nicolas-Virelizier E, Macon WR, Peix M, Micallef IN, Sebban C, Nowakowski GS, Porrata LF, Weiner GJ, Witzig TE, Habermann TM, Link BK Utility of routine post-therapy surveillance imaging in diffuse large B-cell lymphoma. *J Clin Oncol* 2014 Nov;32(31):3506-12. Epub 2014 Sep 29. .

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111. El-Galaly TC MK, Bøgsted M, Brown P, Rossing M, Gang AO, Haglund A, Arboe B, Clausen MR, Jensen P, Pedersen M, Bukh A, Jensen BA, Poulsen CB, d'Amore F, Hutchings M Role of routine imaging in detecting recurrent lymphoma: A review of 258 patients with relapsed aggressive non-Hodgkin and Hodgkin lymphoma. *Am J Hematol* 2014;89(6):575. Epub 2014 Feb 24. .
112. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* 1995;333(23):1540-1545.
113. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy in Relapsed or Refractory Diffuse Large B-Cell Lymphoma: The ORCHARRD Study. *J Clin Oncol.* 2017;35(5):544-551.
114. Chopra R, Goldstone AH, Pearce R, et al. Autologous versus allogeneic bone marrow transplantation for non-Hodgkin's lymphoma: a case-controlled analysis of the European Bone Marrow Transplant Group Registry data. *J Clin Oncol.* 1992;10(11):1690-1695.
115. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol.* 2014;32(31):3490-3496.
116. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol.* 2010;28(27):4184-4190.
117. Gisselbrecht C, Schmitz N, Mounier N, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol.* 2012;30(36):4462-4469.
118. Ng AK, Yahalom J, Goda JS, et al. Role of Radiation Therapy in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group. *Int J Radiat Oncol Biol Phys.* 2018;100(3):652-669.
119. Chen YB, Lane AA, Logan B, et al. Impact of conditioning regimen on outcomes for patients with lymphoma undergoing high-dose therapy with autologous hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2015;21(6):1046-1053.
120. Dickinson M, Hoyt R, Roberts AW, et al. Improved survival for relapsed diffuse large B cell lymphoma is predicted by a negative pre-transplant FDG-PET scan following salvage chemotherapy. *Br J Haematol.* 2010;150(1):39-45.
121. Filmont JE, Gisselbrecht C, Cuenca X, et al. The impact of pre- and post-transplantation positron emission tomography using 18-fluorodeoxyglucose on poor-prognosis lymphoma patients undergoing autologous stem cell transplantation. *Cancer.* 2007;110(6):1361-1369.
122. Roland V, Bodet-Milin C, Moreau A, et al. Impact of high-dose chemotherapy followed by auto-SCT for positive interim [18F] FDG-PET diffuse large B-cell lymphoma patients. *Bone Marrow Transplant.* 2011;46(3):393-399.
123. Terasawa T, Dahabreh IJ, Nihashi T. Fluorine-18-fluorodeoxyglucose positron emission tomography in response assessment before high-dose chemotherapy for lymphoma: a systematic review and meta-analysis. *Oncologist.* 2010;15(7):750-759.
124. Vose JM, Zhang MJ, Rowlings PA, et al. Autologous transplantation for diffuse aggressive non-Hodgkin's lymphoma in patients never achieving remission: a report from the Autologous Blood and Marrow Transplant Registry. *J Clin Oncol.* 2001;19(2):406-413.
125. Thieblemont C CB. Lymphoma in older patients. *J Clin Oncol* 2007;25(14):1916. .
126. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. *N Engl J Med.* 2017;377(26):2531-2544.
127. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *N Engl J Med.* 2019;380(1):45-56.

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128. Papageorgiou ES TP, Dimopoulos M, Pavlidis N, Fountzilas G, Papageorgiou S, Economopoulos T, Hellenic Cooperative Oncology Group. Combination chemotherapy with gemcitabine and vinorelbine in the treatment of relapsed or refractory diffuse large B-cell lymphoma: a phase-II trial by the Hellenic Cooperative Oncology Group. *Eur J Haematol* 2005;75(2):124. .
129. Moccia AA, F. Hitz, P. Hoskins. Gemcitabine, dexamethasone, and cisplatin (GDP) is an effective and well-tolerated salvage therapy for relapsed/refractory diffuse large B-cell lymphoma and Hodgkin lymphoma. *Leuk Lymphoma.* 58(2):324-332.
130. Crump M, J. Kuruvilla, S. Couban,. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. *J Clin Oncol.* 32(31):3490-3496.
131. Mounier N, T. El Gnaoui, H. Tilly,. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large B-cell lymphoma who are not candidates for high-dose therapy. A phase II Lymphoma Study Association trial. *Haematologica.* 98(11):1726-1731.
132. Lopez A, A. Gutierrez, A. Palacios. GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: a phase II study. *Eur J Haematol.* 80(2):127-132.
133. Chao NJ RS, Horning SJ CEPP(B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. *Blood* 1990;76(7):1293. .
134. Sehn LH HA, Flowers CR, Kamdar MK, McMillan A, Hertzberg M, Assouline S, Kim TM, Kim WS, Ozcan M, Hirata J, Penuel E, Paulson JN, Cheng J, Ku G, Matasar MJ Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. *J Clin Oncol* 2020;38(2):155. Epub 2019 Nov 6. .
135. Ivanov V CD, Chetaille B, Esterni B, Olive D, Aurran-Schleinitz T, Schiano JM, Stoppa AM, Broussais-Guillaumot F, Blaise D, Bouabdallah R Efficacy and safety of lenalinomide combined with rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma. *Leuk Lymphoma* 2014 Nov;55(11):2508-13. Epub 2014 Mar 17. .
136. Vitolo U, Witzig TE, Gascoyne R, et al. ROBUST: First report of phase III randomized study of lenalidomide/R-CHOP (R2-CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. *Hematol Oncol.* 2019;37(52):36-37.
137. Younes A, Sehn LH, Johnson P, et al. Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma. *J Clin Oncol.* 2019;37(15):1285-1295.
138. Davies A, Cummin TE, Barrans S, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. *Lancet Oncol.* 2019;20(5):649-662.
139. NHMRC levels of evidence and grades for recommendations for developers of guidelines. In: Council NHaMR, ed. https://www.nhmrc.gov.au/sites/default/files/images/NHMRC%20Levels%20and%20Grades%20(2009).pdf2009.
140. Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol.* 2014;32(27):3048-3058.
141. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2015;26 Suppl 5:v116-125.
142. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. *Br J Haematol.* 2016;174(1):43-56.

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143. Martin A, Conde E, Arnan M, et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. *Haematologica.* 2008;93(12):1829-1836.
144. Pavlu J, Auner HW, Ellis S, et al. LACE-conditioned autologous stem cell transplantation for relapsed or refractory diffuse large B-cell lymphoma: treatment outcome and risk factor analysis from a single centre. *Hematol Oncol.* 2011;29(2):75-80.
145. Kebriaei P, Madden T, Kazerooni R, et al. Intravenous busulfan plus melphalan is a highly effective, well-tolerated preparative regimen for autologous stem cell transplantation in patients with advanced lymphoid malignancies. *Biol Blood Marrow Transplant.* 2011;17(3):412-420.

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TABLES AND FIGURES

Table and figure legend

TABLE 1: Recommended immunohistochemical testing of DLBCL

TABLE 2: Work-up and staging

ECOG: Eastern cooperative oncology group performance status. LDH: Lactate dehydrogenase. CNS: Central nervous system. CSF: Cerebral spinal fluid.

TABLE 3: Lugano classification of lymphoma staging

TABLE 4: International prognostic index (IPI) and subsequent variations

R-IPI: Revised-International Prognostic Index. NCCN National Comprehensive Cancer Network. LDH: Lactate dehydrogenase; ULN: Upper limit of normal; ECOG: Eastern cooperative oncology group performance status; CNS: Central nervous system; GI: gastrointestinal. OS: Overall survival

TABLE 5A: Lymphoma salvage chemotherapy regimens

AutoHCT: Autologous Haematopoietic Cell Transplant. R-GDP: Rituximab, gemcitabine, dexamethasone, cisplatin. R-ICE: Rituximab, ifosphamide, carboplatin, etoposide. R-DHAP: Rituximab, dexamethasone, cytarabine, cisplatin. R-ESHAP: Rituximab, etoposide, methylprednisolone, cytarabine, cisplatin.

TABLE 5B: Autologous transplant conditioning regimens

PFS: progression-free survival, OS: Overall survival. BEAM: Carmustine, etoposide, cytarabine, melphalan. LACE: Lomustine, cytarabine, cyclophosphamide, etoposide. BuMel: Busulphan, melphalan. BCNU: Carmustine.

FIGURE 1: Hans Classification of DLBCL phenotype

Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry

FIGURE 2: Relationship between Cell of Origin, antigen expression and chromosomal rearrangements.

GC-DLBCL: germinal centre-Diffuse Large B-Cell Lymphoma. non-GC-DLBCL-non-germinal-centre-DLBCL. DHL-Double hit lymphoma.

Table 1: Recommended immunohistochemical workup of DLBCL

Marker	% positive	Utility
CD20	>95%	Confirm B cell lineage, predicts sensitivity to Rituximab
PAX5	>95%	Confirm B cell lineage
CD10	30-50%	Suggests germinal centre subtype
MUM1	35-65%	Suggests post-germinal centre subtype (in absence of CD10)
BCL6	60-90%	Suggests germinal centre subtype (in absence of MUM1)
C-MYC	~30-40%	Confers inferior prognosis when expressed with BCL2
BCL2	~50-60%	Confers inferior prognosis when expressed with C-MYC
EBER-ISH	~5% in Western population	
CD5	5-10%	Defines CD5+ DLBCL
Ki67	Variable staining	Confirms high proliferation rate
CD30	10-20%	Common in anaplastic variant, prognostic relevance, therapeutic implications
Cyclin D1	0%	Excludes blastic mantle cell lymphoma

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Table 2. Work-up and staging

History	Presence of 'B' symptoms ECOG performance status History of immunosuppression Prior malignancy and chemotherapy (especially anthracycline) exposure
Physical examination	Involved nodal and extranodal sites Testicular examination in men
Blood tests[9,140-142]	FBE with film and flow cytometry to exclude circulating lymphoma Standard biochemistry (including calcium and phosphate), liver function, LDH, uric acid, beta-2 microglobulin, serum protein electrophoresis. Serology for HIV, Hepatitis B and C, EBV (plus PCR in cases of suspected immunosuppression-related DLBCL) Pregnancy test in women of child-bearing potential
Cardiac assessment	Transthoracic echocardiogram or gated heart pool scan for assessment of left ventricular ejection fraction
Imaging[9,140]	FDG-PET + CT (staged by Lugano classification, table 3) Contrast-enhanced CT in addition to FDG-PET in selected cases
CNS assessment[10]	MRI brain +/- spine and lumbar puncture for CSF cytology and flow cytometry in patients at risk of secondary CNS disease sufficient to justify prophylaxis (see CNS prophylaxis section)
Bone marrow aspirate and trephine[11]	FDG-PET has largely obviated the need for marrow assessment in DLBCL. It is still recommended in selected cases where the discovery of discordant marrow involvement would alter management

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Table 3. Lugano classification of lymphoma staging

Stage	Involvement	Extranodal status
Stage I (limited)	One node or group of adjacent nodes	Single extranodal lesion without nodal involvement
Stage II (limited)	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal with limited continguous extranodal involvement
Stage II bulky	As above with one lesion ≥7.5cm	
Stage III	Nodal disease above and below the diaphragm with spleen involvement	Not applicable
Stage IV	Additional non-contiguous extranodal involvement	Not applicable

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Table 4: International prognostic index and subsequent variations

Prognostic Factor	IPI	aaIPI (≤60yrs)	aaIPI (≤60yrs)	R-IPI	NCCN-IPI
Age (years)					
41to 60	0	0	0	0	1
61 to75	1	N/A	N/A	1	2
>75	1	N/A	N/A	1	3
Normalised serum LDH					
>1 to ≤3 x ULN	1	1	1	1	1
>3x ULN	1	1	1	1	2
ECOG ≥2	1	1	1	1	1
Stage III or IV	1	1	1	1	1
Specific Extranodal sites: bone marrow, CNS, Liver/GI tract or lung	0	0	0	0	1
Any extranodal disease (>1 total)	1	0	0	1	0
	Risk group				
	Low: 0-1 (5yr OS 73%) Low-intermediate: 2 (5yr OS 51%) High-intermediate: 3 (5yr OS 43%) High: 4-5 (5yr OS 26%)	Low: 0 (5yr OS 83%) Low-intermediate: 1 (5yr OS 69%) High-intermediate: 2 (5yr OS 46%) High: 3 (5yr OS 32%)	Low: 0 (5yr OS 83%) Low-intermediate: 1 (5yr OS 69%) High-intermediate: 2 (5yr OS 46%) High: 3 (5yr OS 32%)	Very good: 0 (4yr OS 94%) Good: 1-2 (4yr OS 79%) Poor: 3-5 (4yr OS 55%)	Low: 0-1 (5yr 96%) Low-intermediat 2-3 (5yr OS 82%) High-intermediat 4-5 (5yr OS 64%) High: ≥6 (5yr 33%)

LDH: Lactate dehydrogenase; ULN: Upper limit of normal; ECOG: Eastern cooperative oncology group performance status; CNS: Central nervous system; GI: gastrointestinal

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Table 5a. Lymphoma salvage regimens

Salvage regimens			
Regimen	Overall response rate	CR rate	% received autoHCT
R-GDP[130]	45%	13.5%	51%
R-ICE[116]	63%	36%	51%
R-DHAP[115,116]	44-64%	14-40%	49-55%
R-ESHAP[143]	67%	37%	62%

Table 5b. Autologous transplant regimens

AutoHCT conditioning regimens		
Regimen	PFS	OS
BEAM[119]	47% at 3 yrs	58% at 3 yrs
LACE[144]	42% at 5 years	47% at 5 years
BuMel[145]	64% at 2 years	67% at 2 years
Stanford BCNU[119]	39% at 3 yrs	43% at 3 yrs

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Figure 1: Hans Classification of DLBCL phenotype

Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray.

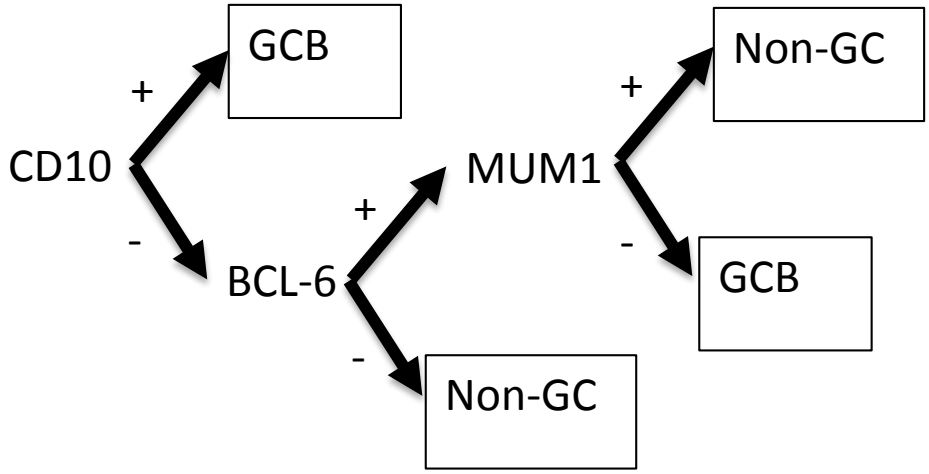

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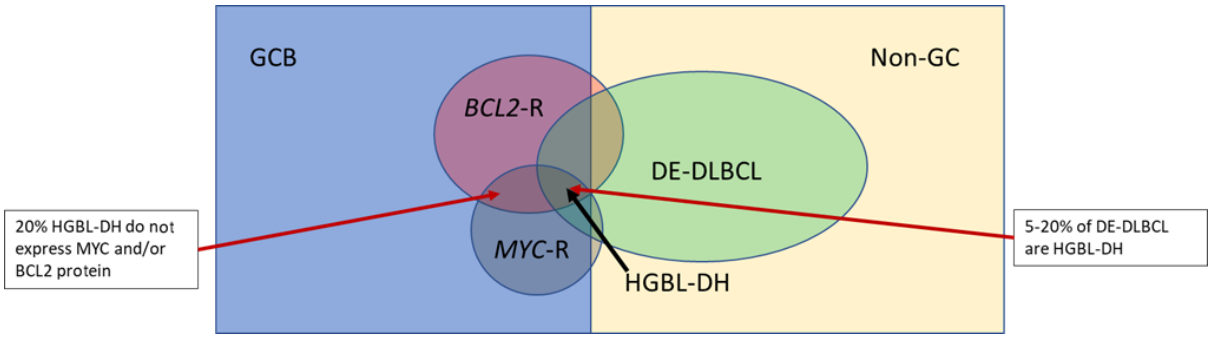
FIGURE 2: Relationship between Cell of Origin, antigen expression and chromosomal rearrangements.



GCB: germinal centre-Diffuse Large B-Cell Lymphoma. non-GC: non-germinal-centre-DLBCL. HGBL-DH: High-grade B cell lymphoma with rearrangements of MYC and/or BCL2 and BCL6.

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SUPPLEMENTARY MATERIAL

Metholodology

The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the NHMRC evidence hierarchy shown in Supplementary tables 1 and 2.[139] Statements without grading were considered justified standard clinical practice by the experts and the ALA members. The manuscript has been subjected to an anonymous peer review process.

SUPPLEMENTARY TABLE 1: Levels of Evidence

Level	Body of Evidence
I	A systematic review of level II studies
II	A randomised controlled trial
III-1	A trial with an independent blinded comparison with a valid reference standard
III-2	A comparative study with concurrent controls e.g. nonrandomised trial, cohort or case control study
III-3	A comparative study without concurrent controls, e.g. historical control study, or 2 or more single arm study
IV	Case series with post-test outcomes

*Adapted from NHMRC Evidence Hierarchy Table 2009

SUPPLEMENTARY TABLE 2: Grades of recommendations

Grade of Recommendation	Description
A	Body of evidence can be trusted to guide clinical practice
B	Body of evidence can be trusted to guide clinical practice in most situations
C	Body of evidence provides some support for recommendation(s), but care should be taken in its application

D	Body of evidence is weak, and recommendation must be applied with caution

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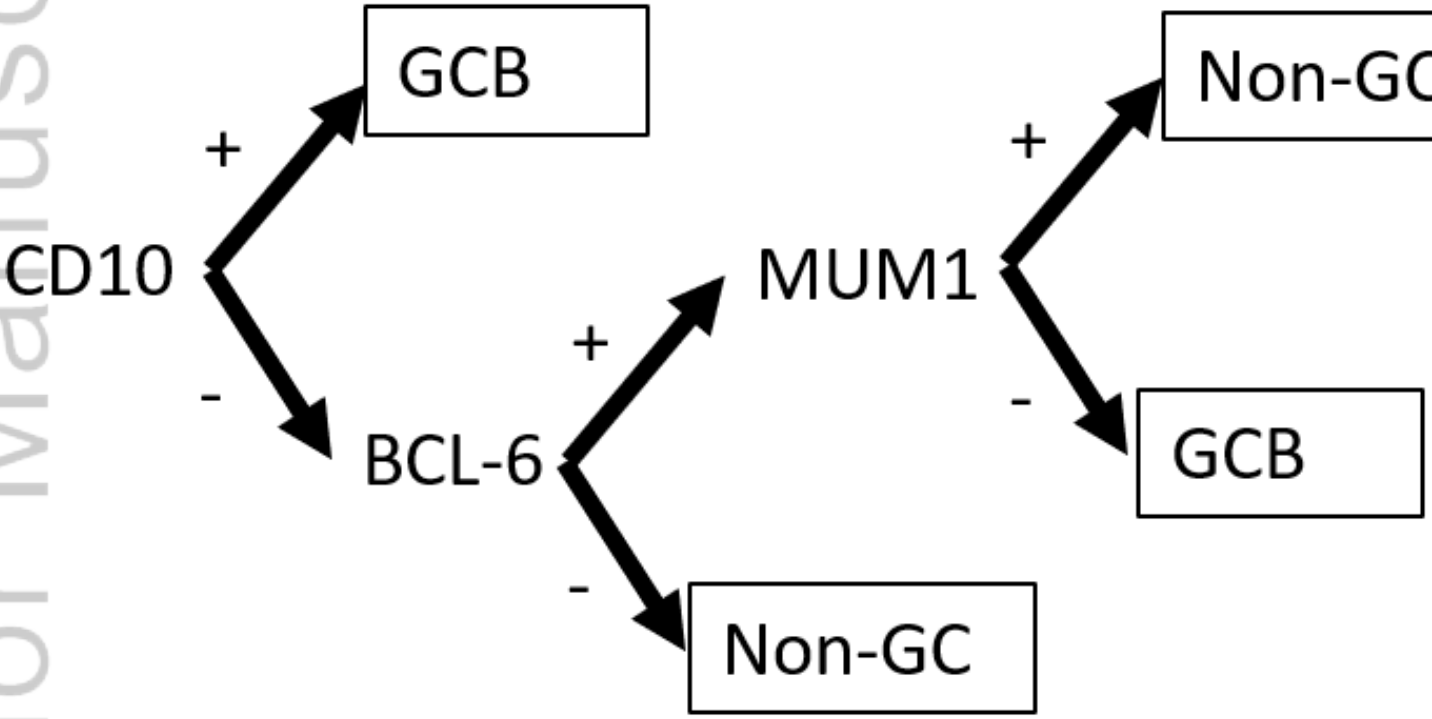

Figure 1.bmp

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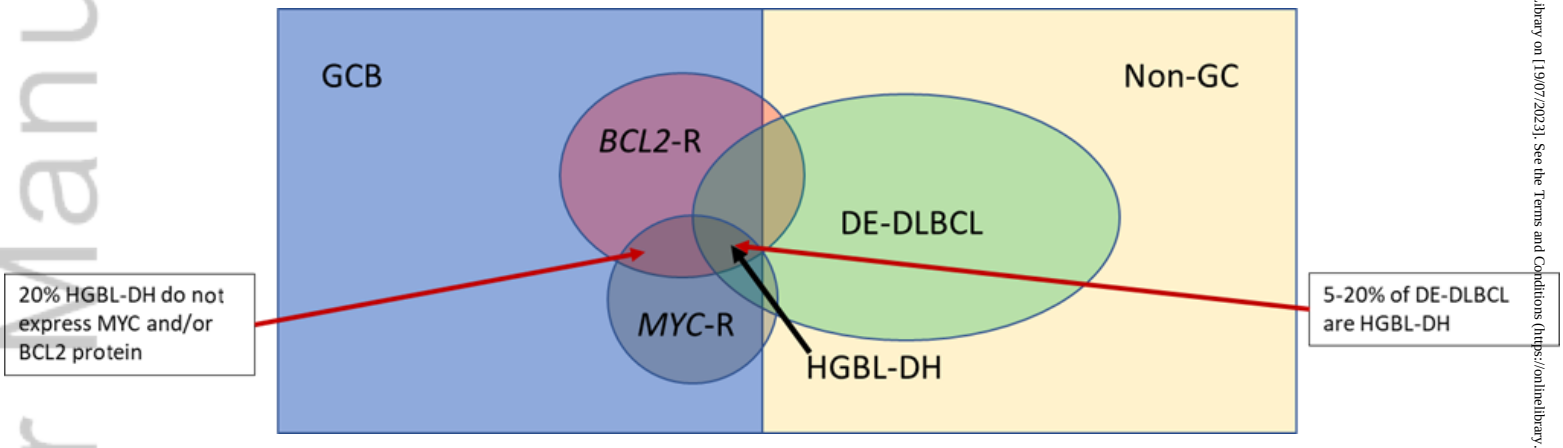

Figure 2 fixed.bmp

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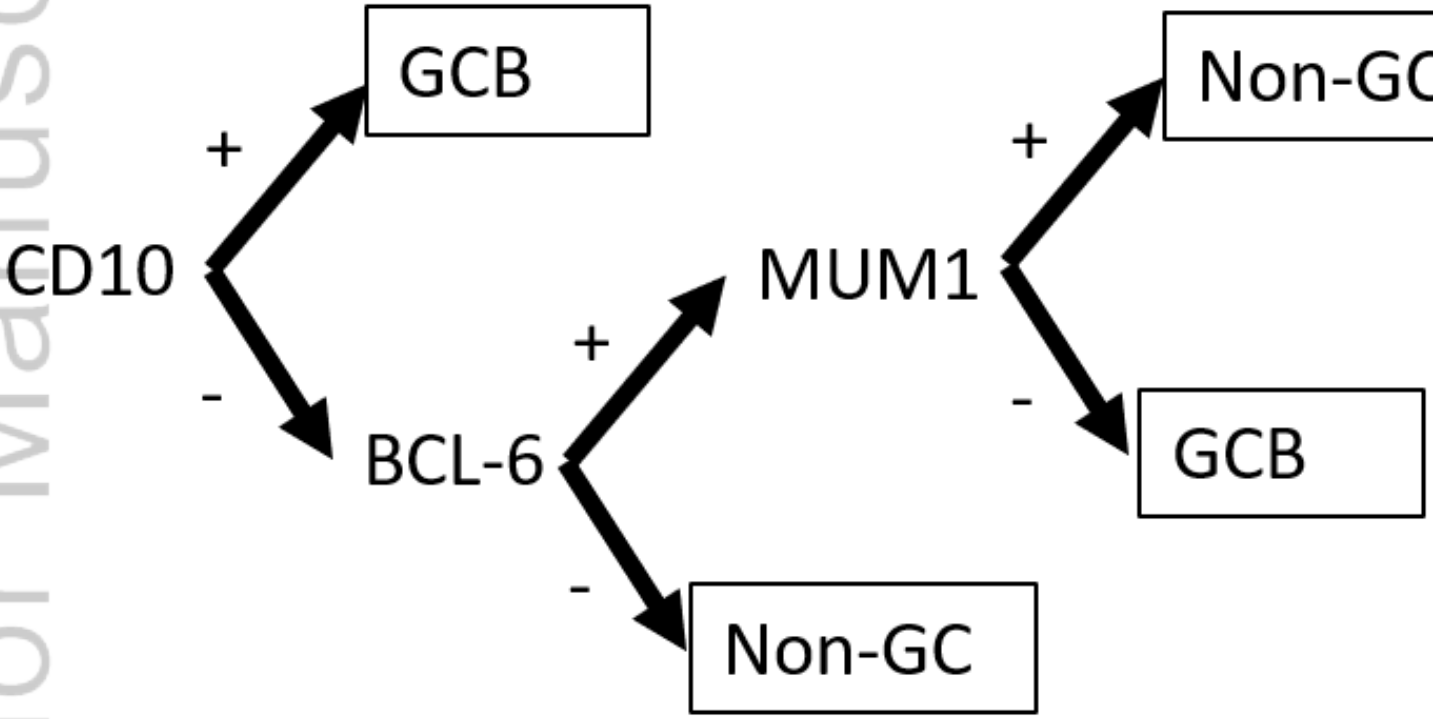

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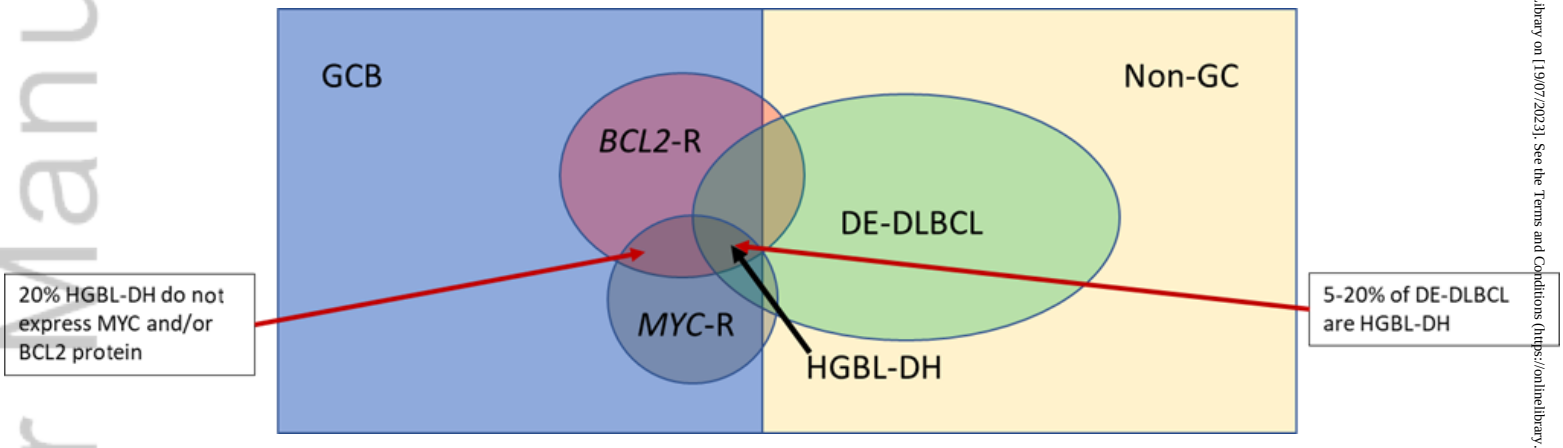

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